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PRINCIPAL INVESTIGATOR: Heiddis Valdimarsdottir, Ph.D.

CONTRACTING ORGANIZATION: Sloan-Kettering Institute for Cancer Research
New York, New York 10021

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Heiddis Valdimarsdottir, Ph.D.

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New York, New York 10021

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To date, 220 women have been recruited for the Naturalistic Study. The data are currently being verified. It is anticipated that during year 4 of the study the data will be analyzed and papers will be submitted for publication and presentation at scientific conferences.

To date, 62 women have been recruited for the Experimental Study. In year 4 we will continue recruiting women into the experimental study and expect to have a total of 100 subjects at the end of year. Data entry and data verification will continue and results will be submitted for presentation at scientific conferences and/or submitted for publication.

We had anticipated that the present research would be further a long than it is. One of the main reasons for the delay has been that the funding (ACS) supporting the present study ran out this year. However, we were successful in getting funding from NIMH which should allow us to continue and complete both the Naturalistic and the Experimental studies.

With the support from this award # 17-94-J-4139 we have published 2 papers, 1 additional paper is in press, and 3 abstracts are published (see Appendix).

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## Introduction

Healthy women with family histories of breast cancer, who are at increased risk for developing the disease, have been reported to have reductions in immune function (reduced natural killer cell activity) compared to women without family histories of cancer in their families (Strayer, Carter & Brodsky, 1986). Consistent with theories of immune surveillance against neoplastic disease (Trinchieri, 1990), such reductions could contribute to the increased risk of breast cancer in women at familial risk for breast cancer. The reduced natural killer (NK) cell activity in women with family histories of breast cancer have previously been attributed solely to heritable deficits in immune function. However, the cumulative evidence that psychological factors (e.g., distress) can affect immune function (see review by Herbert & Cohen, 1993) suggests two ways in which psychoimmune mechanisms may contribute to the immune deficits in these women. First, as women at familial risk for breast cancer have been reported to be more distressed (see review by Lerman & Schwartz, 1993), distress induced immune suppression may contribute to their immune deficits. Second, women at familial risk for breast cancer may be psychobiologically more reactive and/or immunologically more sensitive to psychological challenges.

Two interrelated studies, one naturalistic and another experimental are being conducted to address these issues.

## Body

**The Naturalistic Study**: This study seeks to examine the contribution of distress-induced immune alterations to the reduced NK cell activity in healthy women with family histories of breast cancer. Three major questions are being addressed: First, are healthy women, who are at familial risk for breast cancer, more psychologically distressed than women at normal risk (with no history of cancer in their families)? Second, do healthy women at increased familial risk for breast cancer also show evidence of reduced NK cell activity? Third, does increased emotional distress contribute to the reductions in NK cell activity associated with familial risk for breast cancer?

Procedure: Women with family histories of breast cancer in first degree relatives (Risk Group) and women without family histories of breast cancer in first or second degree relatives (Comparison Group) are being recruited. These women are assessed on three separate days approximately one month apart (controlling for possible effects of menstrual cycles), at the same time of day (controlling for circadian effects). One woman from each of the Groups are assessed concurrently. At each of these assessments subjects complete standardized questionnaires (see study measures section 4.6 in the grant application), and after at least 30 minutes of rest, blood samples are collected for immune and endocrine measures (see sections 4.8 and 4.9 in the grant application).

Results: Since the last report, we have recruited 69 women with (N=34) and without (N=35) family histories of cancer. As indicated in Statement of Work we proposed to have recruited 240 women by the end of Year 3 and we are quite close to that goal as to date 220 women have been recruited for the Naturalistic Study. Of the 220 women, 44 women did not donate blood for immune assessments. The immune and psychological data have been entered for all of the women. However, as this is a large data base, and data entry personnel was never explicitly budgeted in our research support, it has taken us longer to verify the data than we anticipated. Consequently, we are behind in statistical analyses and in preparing manuscripts for publications (see Statement of Work). As the data have yet to be fully verified, it would be premature at the present time to report the results in this progress report as the results may not be accurate. During year 4, we anticipate that all the data will be fully verified which will allow us to address study hypotheses, and prepare and submit manuscripts for publications..

**The Experimental Study:** This study seeks to examine the possibility that increased psychophysiological reactivity and/or immunological sensitivity to psychological challenges could contribute to the reduced natural cytotoxic activity in healthy women with family histories of breast cancer. Three major questions are being addressed: First, do healthy women at increased familial risk for breast cancer also show increased psychological reactivity to experimental stressors (mental tasks)? Second, do healthy women with family histories of breast cancer evidence greater immunologic sensitivity to experimentally-induced distress? Third, is the increased immunological sensitivity to distress in healthy women at increased familial risk for breast cancer due to differences in sympathetic responses and/or cortisol responses to the experimental stressors?

Procedure: Women who have completed the Naturalistic study are recruited for the experimental study. On the experimental days, participants are exposed to two consecutive mental tasks that have been shown to affect psychophysiological reactivity (i.e., self-reported distress, cardiovascular changes, endocrine changes) as well as immune measures (i.e., NK cell activity, lymphocyte proliferation) (e.g., Manuck, Cohen, Rabin et al., 1991; Stone, Valdimarsdottir, Katkin et al., 1993). Psychological distress is assessed (Profile of Mood States and Visual analog Scale; see Section 4.6 in the grant application) and blood samples for immune and endocrine assessments (see Sections 4.8 an 4.9 respectively in the grant application) are collected after a resting period and during and after stressor exposure at 15 to 30 minute intervals. Cardiovascular activity is assessed throughout the session.

Results: A total of 62 women have been recruited to the Experimental study. Since last progress report 20 women with (N=8) and without (N=12) family histories of cancer have been recruited to the Experimental study. All of the women have completed at least one of the longitudinal assessments. In accordance with our Statement of Work (see grant application) data are being entered and verified. In addition we have analyzed some of the data and results have been presented at scientific conferences (see Appendix). Supporting one of our study hypotheses, initial data analyses suggest that women with family histories of breast cancer are

psychobiologically and immunologically more reactive to laboratory stressors than women without family histories of breast cancer (see Appendix).

## Conclusions

**The Naturalistic Study:** To date, 220 women have been recruited for the Naturalistic Study. The data are currently being verified. It is anticipated that during year 4 of the study the data will be analyzed and papers will be submitted for publication and presentation at scientific conferences.

**The Experimental Study**: To date, 62 women have been recruited for the Experimental Study. In line with our proposed Statement of Work (see grant application), we will continue recruiting women into the experimental study, and expect to have a total of 100 subjects at the end of year 4 of the study. Data entry and data verification will continue and results will be submitted for presentation at scientific conferences and/or submitted for publication.

**Summary:** In the Statement of Work (see grant application) we anticipated that the present research would be further a long than it is. One of the main reasons for the delay has been that the funding (ACS) supporting the present research ran out this year. However, we were successful in getting funding from NIMH which should allow us to continue and complete the research.

With the support from this award # 17-94-J-4139 we have 2 published papers, 1 paper in press, and 3 published abstracts (see Appendix).

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# Appendices

**CHANGES IN MOOD ARE ASSOCIATED WITH CHANGES IN NATURAL KILLER CELL ACTIVITY FOLLOWING ACUTE LABORATORY STRESSORS**

Sandra G. Zakowski, Heiddis B. Valdimarsdottir, Julie Fasano, Zakera Gandhi, Libing Chen, Geri Waldman, Dana H. Bovbjerg. Memorial Sloan-Kettering Cancer Center, NY, NY.

Acute experimental stressors have been repeatedly shown to induce increases in natural killer cell activity (NKCA). The role of concurrently induced changes in positive and negative moods in the stress-immune relationship is still unclear. The present study examined these relations in 42 healthy women. After i.v. insertion subjects rested for 30 minutes and were then exposed to a speech task and a mental arithmetic task for a total of 15 minutes. Blood samples were taken at 6 timepoints, at 0' (baseline), 15' (after the tasks), 30', 45', 95', & 105'. NKCA was measured using a well-established whole blood method at 4 different dilutions. Subjects completed the Profile of Mood States (POMS) at baseline and immediately after the tasks.

Analyses yielded the expected post-stressor increase in NKCA as well as total mood disturbance (POMS) ($p<.05$). Examination of the negative and positive mood subscales showed an increase in negative and a decrease in positive mood ($p's<.05$). Increases in total mood disturbance and in negative mood were associated with increased NKCA; Further support for this relation was provided by a significant negative association between changes in positive mood and NKCA ($p's<.05$).

The results are consistent with the view that mood changes may be responsible for the NKCA changes observed in response to experimental stressors. Future experimental studies should explicitly examine the relations between self-reported moods and changes in immune function as a potential pathway to understanding the relations between affective states and disease processes.

Psychosomatic Medicine 1997; 59:82.

**HOSTILE AND DEPRESSED MOODS ARE ASSOCIATED WITH HIGHER NATURAL KILLER CELL ACTIVITY IN HEALTHY WOMEN**

Sandra G. Zakowski, Heiddis B. Valdimarsdottir, Julie Fasano, Zakera Gandhi, Libing Chen, Geri Waldman, & Dana H. Bovbjerg. Memorial Sloan-Kettering Cancer Center, NY, NY.

Several experimental studies have shown that short-term stressors induce both psychological distress and elevations in natural killer cell activity (NKCA). In naturalistic studies, however, possible relations between self-reported distress and NKCA have rarely been investigated. Moreover, the possible selective effects of specific mood states have received little research attention.

To address these issues we assessed moods and NKCA in 45 healthy women. To eliminate acute effects of venipuncture, blood samples were collected for assessment of NKCA 20 minutes after placement of an i.v. catheter. Immediately before the blood draw, subjects completed the Profile of Mood States (POMS) for how they felt "right now". Women also completed the Beck Depression Inventory (BDI), the Brief Symptom Inventory (BSI), and the NEO-Five Factor Inventory.

Regression analysis showed that high total mood disturbance scores (POMS) were associated with high levels of NKCA. Examination of the 6 POMS mood subscales revealed that these effects were specific to depressed and hostile moods ($p's<.05$). The acute nature of these mood effects was confirmed by controlling for longer-term depression (BDI, BSI), hostility (BSI), and neuroticism (NEO).

Results suggest that psychoimmune relations may be more selective than previously appreciated, emphasizing the importance of examining specific mood states. That the mood effects could not be explained by traits or more chronic emotions shows that acute mood states may be important factors to take into consideration in PNI.

Psychosomatic Medicine 1997; 59:98.

# HEIGHTENED PSYCHOBIOLOGICAL REACTIVITY TO LABORATORY STRESSORS IN HEALTHY WOMEN AT FAMILIAL RISK FOR BREAST CANCER

Heiddis B. Valdimarsdottir[1,2], Dana H. Bovbjerg[1,2], Sandra G. Zakowski[1] and Jean Mamakos[2] [1]Memorial Sloan-Kettering Cancer Center and [2]Cornell University Medical College, New York, New York, 10021

Individuals undergoing chronic life stressors have been hypothesized to be more psychobiologically reactive to acute stressors in their lives. Consistent with this possibility, these individuals have been reported to have higher levels of emotional distress and cardiovascular activity following laboratory stressors. The present study tested the hypothesis that the chronic threat of cancer might increase psychobiological reactivity among women at familial risk for breast cancer.

After a 30 minute rest period, 14 healthy women (aged 25-50) at familial risk for breast cancer (Risk Group) and 28 women at normal risk (Comparison Group) were exposed to two classic laboratory stressors (a speech task and mental arithmetic) over a 15 minute interval. Negative moods (visual analog scales) and NKCA were assessed before and after the stressors. Cardiovascular activity was assessed throughout the session.

As expected, there were significant increases in negative mood, cardiovascular activity and NKCA following exposure to the stressors (p's $\leq .05$). Supporting the study hypothesis, these effects were more pronounced in the Risk Group. These women had larger increases in: negative moods (p's $\leq .05$), heart rate ($p \leq .01$), systolic blood pressure ($p \leq .02$), and NKCA ($p \leq .04$). We were unable to account for these differences on the basis of demographic variables or variability in baseline measures.

These results support the view that the chronic threat of cancer in individuals at familial risk is associated with increased psychobiological reactivity to acute stressors in their lives. The data thus suggest that the chronic distress associated with familial cancer risk may not only affect cancer surveillance behaviors, as previously reported, but may also have negative health consequences through changes in psychobiological reactivity.

CORRESPONDING AUTHOR: Dr. Dana H. Bovbjerg, Box 457, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021.

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# PSYCHOSOCIAL FACTORS AND SECRETORY IMMUNOGLOBULIN A

**Heiddis B. Valdimarsdottir**
Department of Psychiatry
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10021

**Arthur A. Stone**
Department of Psychiatry and Behavioral Sciences
State University of New York
Stony Brook, New York 11794

**ABSTRACT:** This review focuses on studies that have examined the relation between psychosocial factors and secretory immunoglobulin A (s-IgA). Several studies have examined the relation between s-IgA and stressful circumstances ranging from major life events to minor daily events. The findings from these studies were often contradictory, since different experimenters reported different stress-related changes in s-IgA. The effects of stress reduction interventions, such as relaxation and imagery, on s-IgA levels have also been examined. Although these studies indicate that various interventions are associated with increases in s-IgA levels, methodological refinements are needed before more definitive conclusions can be made. The possibility that the relation between stress and s-IgA may be moderated by personality characteristics or mediated by psychological distress was supported in some studies. The review concludes with suggestions for future research.

**Key words.** Psychoneuroimmunology, secretory immunoglobulin A, distress, emotions, stress.

## *Introduction*

In the late 1970s, behavioral medicine was defined as a discipline that would investigate the interplay between psychological factors and somatic health and disease (Schwartz and Weiss, 1978). Of course, movements exploring closely associated topics, such as the psychosomatic medicine movement, pre-dated and formed the groundwork for behavioral medicine. Interest in behavioral medicine has grown tremendously, spawning a number of societies and well over a dozen specialized journals.

As behavioral medicine research grew, research efforts shifted from the initial step of demonstrating relations between psychological or social factors and somatic outcomes to hypothesizing about and testing mediational pathways responsible for the observed associations. There are many models that have been proposed that summarize these relations (see reviews by Krantz *et al.*, 1985; Andersen *et al.*, 1994), one of which was advanced by Cohen and Williamson (1991). According to this model, after an environmental stimulus has occurred (*e.g.*, loss of job), has been appraised (*e.g.*, as threatening to one's well-being), and after an affective response has occurred (*e.g.*, negative mood or depression), a series of behavioral and biological processes may come into play. One of these processes is change in behaviors potentially related to disease. For instance, increased use of alcohol or illicit medications, changes in eating patterns, reduced exercise, and less or poorer sleep have all been shown to relate to stress. One of the biological processes that may be affected by the preceding events is the autonomic nervous system. Changes in sympathetic and parasympathetic tone are related to numerous hormonal changes that are likely to influence susceptibility to disease. The process that is the focus of this review is the immune system. Of course, this system is responsible for keeping pathogens out of the body and for eliminating them once they have entered.

Given the importance of the immune system to health, it is not surprising that scientists with an interest

in behavioral medicine have targeted behavior-immune interactions. The extent of this focus is indicated by the creation of the discipline known as Psychoneuroimmunology (PNI). Several major texts have reviewed the PNI literature, there are societies devoted to the topic, and at least one journal publishes PNI work exclusively.

The work we discuss in this review falls into the domain of PNI and focuses on studies that have examined the relation between psychosocial factors and secretory immunoglobulin A (s-IgA). We first present an overview of s-IgA, followed by a discussion of the measures that have been used to index its activation. Summaries of the substantive work follow and are organized according to the nature of the psychosocial factors that have been manipulated or associated with s-IgA measures. These include stressful circumstances, relaxation and imagery, and psychological characteristics of the individual. A section on the possible mediational role of emotions, serving as a link between psychological factors and s-IgA, follows. A section on future directions for examining the relation between psychosocial factors and s-IgA concludes this review. The studies that were included in this review were identified through computerized search (Medline and PsychLit) and through inspection of reference lists from existing reviews and articles.

## Secretory Immunoglobulin A

A glycoprotein called immunoglobulin A, or IgA, is the major immunoglobulin in the fluids that bathe the mucosal surfaces of the body and those surfaces that are the paths of entry of invading bacteria and viruses into the body (*e.g.*, tears, saliva, gastrointestinal, vaginal, nasal, and bronchial secretions [Tomasi, 1970, 1976; Goldblum, 1990]). Secretory IgA (s-IgA) is different from IgA in serum in that it is much larger (Tomasi, 1976) and probably binds invading organisms more effectively than serum IgA. Most infectious agents enter the body through the mucosal surfaces, and the presence of s-IgA antibodies in the fluids helps to prevent infection, especially of the upper respiratory, intestinal, and urinogenital tracts (Tomasi, 1976; Lamm *et al.*, 1995). For example, studies have shown that s-IgA antibody possesses antiviral activity (Dowdle *et al.*, 1971; Lamm *et al.*, 1995) and can prevent invasion by polio, measles, and rubella viruses (Ogra *et al.*, 1971; Ganguly *et al.*, 1973). In addition, there is evidence that s-IgA can prevent bacterial infections (Heddle and Rowley, 1975) and neutralize bacterial toxin (Waldman *et al.*, 1971; Goldblum, 1990). Secretory IgA is also implicated in dental diseases (Taubman and Smith, 1993). Degradation of s-IgA was associated with localized juvenile periodontitis (Gregory *et al.*, 1992). Similarly, caries-prone persons have been found to have lower salivary IgA concentrations than caries-resistant persons (Lehner *et al.*, 1967; Gregory *et al.*, 1992), and deficiencies in s-IgA have been identified as one of the factors responsible for the frequent oral infections in patients with AIDS (Muller *et al.*, 1992).

## Measurement of s-IgA in Psychoneuroimmunology Studies

The two most commonly used measures of IgA production in the field of psychoneuroimmunology have been s-IgA *concentration* and s-IgA *secretion rate*. Secretory IgA concentration is the amount of total IgA protein that is present in a certain volume of saliva (*i.e.*, μg/mL), whereas s-IgA secretion rate refers to the amount of IgA protein detected *per* unit time (*i.e.*, μg/min).

Although these measures have been used rather frequently in conjunction with psychosocial factors (as will be shown below), questions have been raised about their value as an index of immune system functioning. Stone *et al.* (1987b) discussed several potential problems with measures of s-IgA concentration and secretion rate, including: the effect of saliva flow rate on concentration; a possible deterioration of s-IgA proteins by proteases in the mouth; and, on a conceptual level, the meaning of total s-IgA protein as a measure of immune protection. Jemmott and McClelland (1989), who are the authors of the majority of the studies discussed in Stone *et al.*'s (1987b) paper, replied in a subsequent paper. They argued that salivary flow rate might not be as large a problem, especially in unstimulated collection conditions, that the studies were consistent in the relation of s-IgA changes to psychological factors, that s-IgA might not deteriorate in the mouth, and that total s-IgA protein was shown to be a reasonable measure.

Because these are debated issues (and because we have taken a position on some of these issues), we recommend that readers evaluate the arguments for themselves. However, we would like to comment briefly on the saliva flow issue. As stated above, one of the potential problems with using s-IgA measures is that saliva flow can affect both concentrations of s-IgA and s-IgA secretion rate. At least in some situations, it has been demonstrated that when saliva flow rate is artificially stimulated (with, for example, lemon drops), s-IgA concentrations decrease with increased flow, while the s-IgA secretion rate increases with increased flow rate (Brandtzaeg, 1971). Similar findings have been observed when saliva flow was not artificially stimulated (Graham *et al.*, 1988; Kugler *et al.*, 1992; Evans *et al.*, 1993). The relations between saliva flow rate and s-IgA concentration and secretion rate are particularly important, since autonomic arousal associated with stress or negative affect may influence saliva flow rate (Stone *et al.*, 1987b), although the directionality of the effects is uncertain.

An issue in this debate that has not received much attention concerns the measurement of saliva volume. In our experience, measuring saliva flow is not a straightforward task, and we question the reliability as well as

the validity of such measurement. It is difficult for a subject to drool into a vial, and we speculate that the amount of saliva collected is related to a number of factors concerning how the subject accomplishes the task. We know of no test-retest data demonstrating that flow is a reliable measure. This is an area that deserves some attention in the future.

On conceptual grounds, an alternative to the measurement of all s-IgA protein in a sample of saliva has been proposed by Stone *et al.* (1987b). They argue that the s-IgA antibody response to a particular antigen, rather than s-IgA protein, should be evaluated. One of the antigens that Stone and his colleagues have used in their studies is a harmless protein, rabbit albumin. According to these authors, the antibody responses to a novel antigen (*e.g.*, rabbit albumin in samples of individuals who have not previously eaten rabbit) are analogous to those responses to a pathogen that would occur if an individual were infected by a virus or a bacterium.

To date, there has been no confirmation of the relative merits of the use of total s-IgA vs. specific s-IgA antibody in terms of response to a known antigen, since only the Stone research group has used the latter methodology. Jemmott and McClelland (1989) have raised issues concerning this measure, given that it is based on a ratio of specific antibody to total s-IgA protein. Those authors are concerned that the overall amount of s-IgA—rather than the relative growth of s-IgA antibody—is the important factor. As will be shown below, there are many studies that have shown associations between psychological stressors or other conditions and s-IgA levels, and there have been two separate studies that have shown such associations with s-IgA antibody to a novel antigen. In those studies, both measures of s-IgA were available, and the specific antibody measure demonstrated stronger associations with stress variables than did the total protein measure. Nevertheless, no data are available that address the issue of which is a better empirical predictor of health status.

## *Stressful* Events

Stressful events, ranging from major life events to daily events, have been shown to be related to illness onset in a number of studies (Cohen and Williamson, 1991). From the perspective of understanding the rôle of s-IgA, it is important to note that some of these studies had upper respiratory illness (URI) as the outcome variable. These studies support the idea that life stressors may be related to immunological processes, although compelling arguments can also be advanced that behavioral factors—such as sleeping, alcohol consumption, smoking, etc.—also mediate the stress-illness association (see Cohen *et al.*, 1995). Several studies, reviewed below, examined the possibility that stressful life events (major and daily) affect s-IgA.

### Total event studies

We start with studies that have used event checklists and created predictor variables representing the total amount of stress associated with those events an individual experiences. In general, studies have not found a relation between major life events (*e.g.*, death of a spouse) and s-IgA (Kiecolt-Glaser *et al.*, 1984; Graham *et al.*, 1988) or between daily hassles (defined as minor daily annoyances, but that are usually measured in a retrospective manner over a 30-day period [see Kanner *et al.*, 1981]) and s-IgA (Kubitz *et al.*, 1986; Farne *et al.*, 1994). A complex relation between s-IgA concentration and daily hassles was observed in Martin and Dobbin's (1988) study of daily hassles. In this study, hassles and s-IgA were assessed during two sessions 90 days apart. Frequency of hassles assessed during the first session was negatively correlated with s-IgA concentration assessed in both sessions. On the other hand, no relation was observed between frequency of hassles and s-IgA concentration assessed during the second session.

Two studies have examined how minor stressors measured on a daily basis affect s-IgA. In Evans *et al.* 's (1993) study, subjects completed the Student's Assessment of Daily Experience (SADE) questionnaire daily for 14 days. Each of the 27 events on the SADE that occurred during the day was rated by subjects on a six-point scale from "extremely desirable" to "extremely undesirable". On each day, subjects also provided a timed saliva sample for assessments of s-IgA concentration and s-IgA secretion rate. When the data were aggregated over the two-week period, a negative correlation was observed between undesirable events and s-IgA concentration, and a positive correlation was observed between desirable events and s-IgA concentration. That is, the mean level of s-IgA concentration across all days was negatively correlated with the average number of undesirable events for the same period and positively correlated with the average number of desirable events. A parallel finding was observed for s-IgA secretion rate. On the other hand, analyses examining the day-to-day association between events and s-IgA concentration and secretion rate (within subjects as opposed to the previous between-subjects analyses) revealed that while undesirable events were associated with higher concentrations of s-IgA, undesirable events were unrelated to s-IgA secretion rate. Desirable events were unrelated to both s-IgA concentration and s-IgA secretion rate. These findings are troublesome, since the two types of analyses produced divergent results.

In contrast to Evans' study of total s-IgA, Stone *et al.* (1994) used the specific antigen model of s-IgA. They exposed 94 adult males to a harmless protein (rabbit albumin) and examined whether daily events affected s-IgA antibody response to the rabbit albumin. The immunization procedure involved daily ingestion of a

capsule containing rabbit albumin for 12 weeks. Each day, subjects also completed an 80-item event checklist that was organized in sections dealing with work, leisure, friends, spouse, children, household activities, finances, self, and two write-in items. A further refinement of the event assessment was that subjects' spouses aided them in the accurate completion of the event checklist to ensure the most accurate and objective reports of daily events (see Stone and Neale, 1982, for a description of the questionnaire development). As an assessment of the subjective experience of the event, each event that occurred during the day was rated on a six-point scale, from "extremely desirable" to "extremely undesirable".

After completing the questionnaire, subjects collected saliva that was assayed for s-IgA antibody activity to the rabbit albumin. Results from within-subject analyses revealed that the frequency of desirable events was related to more s-IgA antibody production, whereas the frequency of undesirable events was related to less s-IgA antibody production. In other words, on days when there were relatively more undesirable events than usual, s-IgA antibody levels were lower than on days without undesirable events. The authors also examined whether daily event content predicted s-IgA antibody production. Undesirable work events and desirable leisure and household events were more strongly related to s-IgA antibody than were events in other categories. Last, desirable events on the previous two days predicted subsequent increases in s-IgA antibody production, but for undesirable events, only the same-day events inversely predicted s-IgA antibody production. It is important to note that days with upper respiratory symptoms were eliminated from these analyses; this procedure has not been carried out in other daily studies.

### Single-Event Studies

Rather than investigating how the number of major stressful life events or day-to-day events affects s-IgA, several studies have examined the impact of a single stressful circumstance, academic pressure due to examinations. Two studies reported that academic stress is associated with reductions in s-IgA. Jemmott *et al.* (1983) collected saliva from 47 dental students. Five collections were made over an 11-month period: three collections during examination periods and two during low-stress periods. The authors found that s-IgA secretion rate was lower during the three exam time points compared with the two low-stress time points. Since data collection was spread over an 11-month period, it is possible that these effects were due to seasonal variation in s-IgA secretion. To rule out this possibility, Jemmott and Magloire (1988) conducted a second study using a shorter time interval. Saliva was collected from 15 undergraduates five days prior to their exam, during their exam period, and two weeks after their exam. S-IgA concentration, s-IgA secretion rate, and s-IgA statistically adjusted for saliva flow were lower during the exam period compared with the measures collected before and after the exam.

Increases in s-IgA have also been observed after examination. McClelland *et al.* (1985) found that both s-IgA concentration and norepinephrine concentration in saliva increased in 46 students both immediately after and 1 3/4 hours after an exam, compared with baseline measures collected several days after the exam. The increase in norepinephrine concentration did not account for the increase in s-IgA concentrations, since the correlation between these two measures was nonsignificant. Evans and colleagues (1993) collected saliva from 18 students in two consecutive weeks. In the second week, all students had to give a presentation. During both weeks, saliva was collected 4 times one hour apart, and in the second week, saliva was collected immediately after the presentation. The authors found that there was a trend ($p = 0.10$) for s-IgA secretion rate to increase from week 1 to week 2 to post-presentation. A parallel increase was observed in salivary cortisol concentrations. However, since the authors did not examine the relation between s-IgA secretion rate and salivary cortisol, it is not clear if the increase in salivary cortisol contributed to the increase in s-IgA secretion rate.

No change in s-IgA following an examination has also been observed. Kiecolt-Glaser and colleagues (1984) collected saliva from 65 medical students a month before a final exam and again on the first day of the final exam. No change in s-IgA concentration was observed from pre-test to post-test assessments. Mouton *et al.* (1989) collected saliva from 44 dental students on four occasions over two academic years: two collections during low-stress periods and two collections during examination periods. Results indicated that academic examinations affected s-IgA secretion rate only when the final examination and the summer vacation samples were compared (s-IgA secretion rate was lower during the final examination than during the summer vacation). On the other hand, no difference in s-IgA secretion rate was observed between samples collected during midterm exams and samples collected during midterm break.

### Summary

The pattern of results in these studies is neither consistent nor simple. Many studies that examined major life events and daily hassles used retrospective designs in which subjects indicated how many life events or hassles had occurred over a prior time period. It is therefore possible that recall ability and/or memory biases accounted for the lack of association between s-IgA and life events. The studies that examined the impact of academic stressors on secretory IgA are difficult to evaluate because they differ in several key variables. One of these variables is the timing various experi-

menters chose to collect their pre-stress, stress, and post-stress measures. For example, McClelland *et al.* (1985) collected the baseline measure a few weeks after the exam and the stress measure immediately after an exam and 1 3/4 hours after the exam, whereas Jemmott and Magloire (1988) collected their baseline measure five days prior to the exam and the stress measure during the examination period. It is certainly possible that changes in secretory IgA observed at some of these times might not be present at other times. It is of interest that the two studies (McClelland *et al.*, 1985; Evans *et al.*, 1994) that observed increases in s-IgA following the academic stressor collected their stress measures immediately following the completion of the exam. It is possible that termination of an acute stressor results in increased s-IgA; however, before any conclusion can be reached, studies need to be conducted that will allow for the exploration of timing factors.

Another variable on which these studies differ is the procedure used to determine s-IgA. McClelland *et al.* (1985), for example, measured s-IgA concentration, whereas Mouton *et al.* (1989) measured s-IgA secretion rate. Only two of the studies (Jemmott and Magloire, 1988; Mouton *et al.*, 1989) measured saliva flow rate. Examination stress has been found to affect flow rate (Bates and Adams, 1968), and, as discussed above, s-IgA concentrations and secretion rate are differentially affected by saliva flow rate. Therefore, it is difficult to interpret the findings that did not take saliva flow rate into account, since the effects of stress on saliva flow could have accounted for the changes observed in s-IgA. The mechanism whereby stressful events affect s-IgA is not clear. It has been hypothesized that stress affects the immune system through its impact on the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system (see review by Rabin *et al.*, 1989; Ader and Felten, 1995; Weigent and Blalock, 1995; Bedovsky and Rey, 1996). In the studies reviewed above, changes in salivary cortisol (Evans *et al.*, 1994) and in salivary norepinephrine (McClelland *et al.*, 1985) were observed in parallel to changes in s-IgA levels. However, it is not clear if these stress-induced hormonal changes contributed to the stress-induced changes observed in s-IgA levels, since McClelland *et al.* (1985) found no relation between salivary norepinephrine concentration and s-IgA concentration, and Evans *et al.* (1994) did not examine the relation between salivary cortisol concentration and s-IgA secretion rate.

## Relaxation and Imagery

The evidence that stress can affect the immune system, including s-IgA, raises the possibility that positive experiences, the opposite of stressful ones, could also affect the activity of the immune system (Jasnoski and Kugler, 1987; Zakowski *et al.*, 1989; Van Rood *et al.*, 1993). Several behavioral intervention techniques have been found to influence physiological processes, such as heart rate and blood pressure (Blumenthal and McKee, 1987; Basmajian, 1989). The studies reviewed below examined whether it is possible to increase the levels of s-IgA by stress-reducing interventions.

Green and Green (1987) randomly assigned 50 college students to relaxation groups (relaxation response, guided visualization, back massage) or control groups (lying quietly with eyes closed or touching-control group). Saliva samples were collected before and immediately after the session, which lasted 20 minutes. Results indicated that there was a significant increase in s-IgA concentration from pre- to post-treatment in the relaxation groups, but no change was observed in the control groups. Salivary cortisol was not affected by the relaxation training, suggesting that the changes in s-IgA were independent of changes in cortisol.

In another study, the same authors (Green *et al.*, 1988) examined the effect of daily relaxation on several parameters of the immune system, including s-IgA secretion rate. Forty subjects were randomly assigned to practice one of three relaxation techniques (relaxation response while sitting up, relaxation response while lying down, and guided visualization while lying down) daily for three weeks. Saliva samples were collected before and after 20 minutes of supervised relaxation on day 1 and on day 22 or after three weeks of practicing the relaxation. Since there were no differences among the relaxation groups, the data from the three treatments were combined. In confirmation of previous findings, a significant increase in s-IgA secretion rate was observed immediately after 20 minutes of relaxation practice compared with levels right before the relaxation. In addition, long-term practice effects were also observed: s-IgA secretion rate increased significantly from day 1 to day 22. These changes in s-IgA secretion rate appeared to be independent of psychological distress, since no change was observed in anxiety as measured by the anxiety scale on the Hopkins symptom checklist (Derogatis *et al.*, 1974) and the Taylor manifest anxiety scale (Taylor, 1951).

Jasnoski and Kugler (1987) randomly assigned 30 undergraduates to two relaxation groups or a control group. One of the relaxation groups was trained in progressive relaxation and focused breathing, while the other relaxation group was also trained in imagining powerful, positive immune function. The control group was instructed to discriminate between two tones presented at variable intervals. Saliva samples were collected before and immediately after the training sessions. After a single one-hour session, an increase was observed in s-IgA in both of the relaxation groups, but no change was observed in the control group. Norepinephrine and epinephrine from saliva and serum were also assessed, as was cortisol in saliva. However,

none of these neuroendocrine measures accounted for the s-IgA difference between the relaxation and the control groups.

Rider *et al.* (1990) examined whether imagery directed at biological mechanisms is more effective in increasing s-IgA concentration than non-directed imagery. Forty-five students were randomly assigned to three groups. Members of Group 1 were instructed to focus their imagery on their immune system while they listened to an audio cassette containing imagery instruction followed by music. Group 2 received the same music and general non-specific imagery instructions, and Group 3 underwent no treatment. Subjects came for three sessions scheduled three weeks apart (days 1, 21, and 42), and each session lasted 17 minutes. Saliva samples were collected at the beginning of each session and again at the end of each session. Subjects in the treatment groups were provided with cassette tapes to which they were instructed to listen at home on a bi-daily basis for six weeks.

In both treatment groups, s-IgA concentration increased within each session, yet no change was observed in the control group. Changes in s-IgA concentration across the sessions were not examined; however, inspection of the means suggests that the treatments did not increase s-IgA across sessions. The interventions decreased psychological distress as measured by the Profile of Mood States (McNaire *et al.*, 1971), but no change was observed in sympathetic nervous system response as measured by skin temperature. The treatment groups reported fewer symptoms during the study; however, the particular symptoms affected did not appear to be immune-related (breathing difficulty, jaw clenching, and rapid heartbeat). In their second study, Rider and Welden (1990) used live, improvised music instead of taped music, and only one 10-minute session was conducted. After the intervention, concentrations of s-IgA were higher in the music+imagery group than in either the music-only group or the control group. The music-only group did not differ from the control group.

One study has examined whether relaxation affects s-IgA in children. Olness *et al.* (1989) assigned 57 children to two treatment groups and a control group. During the treatment session, which lasted 25 minutes, both treatment groups learned self-hypnosis. In addition, one of the groups was given specific suggestions to increase salivary immunoglobulins. The control group subjects were engaged in conversation for 25 minutes. Children who received the specific suggestions had significantly higher concentrations of s-IgA after the training session. No change was observed in the other two groups.

Groer *et al.* (1994) examined the effects of a 10-minute massage and back rub on s-IgA concentration and s-IgA secretion rate. Eighteen subjects who were assigned to the experimental group received a 10-minute back massage, and 14 subjects who were assigned to the control group rested for 10 minutes. Although the treatment did not affect anxiety as measured by the Spilberger state/trait anxiety inventory (Spielberger, 1983), an increase in s-IgA concentration was observed in the experimental group, and a similar trend was observed for s-IgA secretion rate.

### Summary

These studies suggest that various interventions can induce short-term increases in s-IgA levels. However, methodological refinements are needed before more definitive conclusions can be made. The long-term effects of these interventions on s-IgA levels are not clear, since most of the studies collected saliva only immediately before and immediately after the intervention. Of the two studies (Green *et al.*, 1988; Rider *et al.*, 1990) that assessed s-IgA a few weeks after their intervention, only one (Green *et al.*, 1988) reported increased levels of s-IgA as long as 22 days after the completion of the intervention. Furthermore, future studies need to assess variables such as frequency of practice and compliance with treatment regimens. Because none of the studies assessed whether the individuals used relaxation skills in stressful situations, there is no experimental evidence that coping (*e.g.*, relaxation) intervenes between stress exposure and s-IgA.

The mechanism whereby these interventions affect s-IgA is not yet clear. It is possible that these interventions affect subjective distress and physiological arousal, which in turn may affect s-IgA. However, of the three studies (Green *et al.*, 1988; Rider *et al.*, 1990; Groer *et al.*, 1994) that assessed subjective distress, only one study (Rider *et al.*, 1990) observed a decrease in subjective distress after the intervention, and the two studies (Green and Green, 1987; Jasnoski and Kugler, 1987) that included neuroendocrine assessments did not observe changes in these measures following the intervention. Clearly, studies are needed that systematically investigate the mechanism underlying the effects of psychosocial interventions on the s-IgA.

One possible confounding factor in these studies is saliva flow rate. Relaxation has been found to affect saliva flow rate (Carlson, 1986), and saliva flow rate can affect both s-IgA concentration and secretion rate. Since none of the investigators corrected their s-IgA measures for flow rate, the possibility that the change in secretory IgA was due to flow rate changes cannot be ruled out.

## Psychological Characteristics of Individuals

In earlier reports on the relationship between stress and illness, it was assumed that stressors affected all individuals similarly. However, since the correlation between stressful life events and illness was found to be generally low, researchers became more interested in moderating and/or mediating variables that might augment or

reduce the effects of stressful variables. The studies reviewed below have examined the possibility that variables that have been shown to moderate the stress and illness association also moderate the relation between stress and s-IgA concentration and secretion rate.

### Sense of Humor

This characteristic has been found to moderate the relation between stressful life experiences and psychological distress (Lefcourt and Martin, 1986). The possibility that sense of humor may also affect s-IgA has been examined in several studies. Martin and Dobbin (1988) examined whether sense of humor moderates the effects of daily hassles on s-IgA concentration. Approximately 90 days apart, 40 undergraduates provided saliva samples and completed a daily hassles scale. In addition, they completed four humor questionnaires (situational humor response, coping humor, sense of humor, and liking of humor). Sense of humor was unrelated to s-IgA concentration, but there was some support for the stress-buffering effects of humor: The negative association between hassles assessed at time 1 and s-IgA concentration assessed at time 2 was stronger for individuals with low scores on the humor questionnaires than for individuals with high scores on the humor questionnaires.

Another way that humor has been explored is shown in an investigation of exposure to humorous stimuli in individuals with a good sense of humor. Dillon *et al.* (1985) observed an increase in s-IgA concentration among 10 subjects immediately after they had watched a humorous videotape but not after they had watched a didactic control tape. Change in s-IgA was inversely related to sense of humor as measured by the Coping Humor Questionnaire (CHQ; Martin and Lefcourt, 1984). On the other hand, in contrast to Martin and Dobbin's (1988) finding, baseline levels of s-IgA were positively related to sense of humor. Similarly, Dillon and Totten (1989), who studied 17 women before and after they gave birth, found a positive association between s-IgA concentration and sense of humor as measured by the CHQ.

Lefcourt *et al.* (1990) conducted three studies to examine the relation among sense of humor, humorous stimuli, and s-IgA. In all three studies, subjects watched humorous movies and provided saliva samples before and after the presentation of the movies. The movie presented and methods to assay s-IgA along with the timing of baseline assessments varied between the studies. In all three studies, subjects completed two humor scales, the Situational Humor Response Questionnaire (SHRQ; Martin and Lefcourt, 1984) and the Coping Humor Scale (CHS; Martin and Lefcourt, 1993). There was an increase in s-IgA from before to after the presentation of the humorous movie in all three studies. None of the studies found a relation between sense of humor and baseline levels of s-IgA. Subjects who scored high on the CHS in study 1 had a significant increase in s-IgA concentration, whereas no change was observed among subjects who scored low on the this scale; this relation was not observed in studies 2 and 3. A marginally significant interaction was found in study 3 between SHRQ and the condition that reflected the greater change for subjects with high SHRQ scores; this interaction was not observed in studies 1 and 2.

Two studies examined the effects of weeping and laughing on s-IgA. Labott *et al.* (1990) showed 32 undergraduate women sad and humorous videotapes. Half of the subjects were told to express their emotions, and half of the subjects were told to inhibit their emotions. Seven control subjects watched documentary tapes. Seven subjects in the expression condition were excluded from the analyses, since they failed to express their emotions overtly, and seven inhibition subjects were excluded, since they expressed their emotions overtly. Individuals who cried during the sad movie had significantly lower s-IgA concentrations after the movie compared with both the control subjects and the subjects who inhibited overt expression of crying. On the other hand, the humorous movie was associated with increased s-IgA concentration regardless of the expression or inhibition of overt laughter. Sense of humor, as assessed by the Coping Humor Questionnaire (Martin and Lefcourt, 1983), was not associated with initial or baseline s-IgA concentration values. To examine further the effects of emotional crying on s-IgA concentration, Martin *et al.* (1993) showed 42 undergraduates a sad movie. An increase was seen in s-IgA from pre- to post-movie in subjects who reported that they had not cried during the movie. No change was seen in s-IgA among subjects who reported that they had had tears in their eyes during the movie or among subjects who reported that they had tears down their faces or sobbed during the movie.

### Inhibited and Stressed Power Motivation

These concepts have been studied extensively by David McClelland and his co-workers. Individuals high in inhibited power motivation are assertive and hard-driving, but inhibited in direct expression of aggression. Such people are more vulnerable to disease than others, especially if they have experienced or are currently under power-related stress (*i.e.*, life events that challenge or threaten the individual's ability to perform powerfully or impress others). In a series of studies, McClelland and colleagues have examined power motivation and s-IgA.

McClelland *et al.* (1980) explored the relation between power motivation, stressful life events, upper respiratory infection, and concentrations of s-IgA. Twenty-seven male college students were assessed twice 48 to 72 hours apart. During the first session,

subjects provided saliva samples and completed a modified version of the Social Readjustment Rating Scale (SRRS; Holmes and Rahe, 1967) and an illness inventory. The items of the SRRS were classified as power events, affiliative events, both, or neither. During the second visit, subjects provided urine samples for assessments of epinephrine and norepinephrine, after which they participated in a mildly stressful task for 2 1/2 hours, followed by additional urine and saliva sampling. Seven subjects were classified as high in need for power, high in inhibition, and high in reported power stress (HHH group). The HHH subjects reported more illnesses in the past 6 to 10 months, had lower s-IgA on the first assessment, and had higher epinephrine excretion rates (assessments before and after the task were averaged) than other subjects. On the other hand, the HHH subjects did not differ from other subjects in norepinephrine excretion rate or in the concentration of s-IgA after the task.

In a similar study with 133 prisoners, McClelland *et al.* (1982) found that prisoners who scored high on need for power and high on life stress had a lower concentration of s-IgA and reported more illnesses in the past 12 months. In contrast to the 1980 study, prisoners who were also high on inhibition had higher concentrations of s-IgA and reported fewer illnesses in the past 12 months than prisoners low on active inhibition.

In two of the examination studies reviewed above, McClelland and co-workers investigated whether examination stress had greater impact on s-IgA among students high in need for power. The first study (Jemmott *et al.*, 1983) assessed s-IgA secretion rate on five occasions (three exam points and two low-stress points) over an 11-month period. A continuing decline in s-IgA secretion rate through the final low-stress period was observed among the students classified as high in need for power and high in active inhibition, whereas s-IgA secretion rate recovered during the low-stress periods in all other subjects. Moreover, students classified as high in need for affiliation and low in active inhibition had higher s-IgA secretion rates on all five assessments compared with all other students. In their second study, McClelland *et al.* (1985) failed to find consistently higher s-IgA levels among individuals classified as high in need for affiliation. A difference in s-IgA concentration after taking an exam was observed between individuals who differed on power motivation: Students whose need for power was stronger than their need for affiliation had lower s-IgA 1 3/4 hours after their exam as compared both with baseline measures collected a few days after the exam and with students whose need for affiliation was higher than their need for power. Students with stronger need for power also had greater increases in norepinephrine in response to the examination, but the increase in salivary norepinephrine was not related to s-IgA concentration.

### Locus of control

This concept is defined as a person's belief that he or she can control desired or undesired outcomes (such individuals have an internal locus of control) or that such outcomes are the results of fate, luck, or other forces (external locus of control). Kubitz *et al.* (1986) examined the relation among health, locus of control, daily hassles, and levels of s-IgA concentration. Twenty-nine subjects provided saliva samples and completed both the Multi-Dimensional Health Locus of Control Scale (MHLC; Wallston *et al.*, 1976), a measure of locus of control over health outcomes, and the Hassles Scale (Kanner *et al.*, 1981), a measure of frequency and intensity of stressful situations in the past month. The results indicated that while there was no relation between levels of s-IgA concentrations and daily hassles, there was an inverse relationship between concentrations of s-IgA and internal locus of control. An interaction between locus of control and daily hassles was also obtained: Individuals high on internality and with high levels of daily hassles had lower levels of s-IgA than individuals low on internality and with high levels of daily hassles. As discussed by the authors, the finding that subjects with more internal locus of control had lower levels of s-IgA was surprising, since several studies have shown that internally oriented individuals report fewer illnesses (Wallston and Wallston, 1982). Last, menstrual cycle status may influence levels of s-IgA, since higher levels of s-IgA were observed for female subjects in the first half of their cycle than for female subjects in the second half of their cycle.

### Hardiness

This concept has been defined as a composite of three tendencies: sense of internal locus of control, sense of purpose and involvement, and a tendency to view changes as incentives or opportunities for growth (Kobasa, 1979, 1982). Several studies have shown that hardiness plays an active role in protecting individuals from stress (Kobasa, 1979, 1982; Kobasa *et al.*, 1981). In the study by Dillon and Totten (1989), reviewed above, hardiness was not related to s-IgA concentration or to upper respiratory tract infection.

### Social support

Among the variables discussed in this section of the paper as having an association with health status, social support has by far received the most empirical support. Generally, the idea is that higher levels of social support are related to positive health outcomes (Cohen and Wills, 1985), but there are more complex hypotheses as well. According to the main-effect hypothesis, social support is beneficial for health regardless of whether the individuals are exposed to stress. Alternatively, according to the buffering hypothesis, social support has a

beneficial effect on health only when individuals are exposed to stress. Existing studies support both of these hypotheses (Cohen and Wills, 1985). The study by Jemmott and Magloire (1988), reviewed above, included a measure of social support. Consistent with the main-effect model, the authors found that students who reported adequate social support had higher concentrations of s-IgA across all three assessments (pre-exam, exam, post-exam). On the other hand, in contrast to the buffering hypothesis, the relation between adequacy of support and s-IgA concentrations did not differ in the exam period compared with the pre- and post-exam periods. Two of the studies reviewed above included measures of loneliness. In both studies, loneliness, which may reflect low social support, was unrelated to s-IgA concentration (Kiecolt-Glaser *et al.*, 1984) and to s-IgA secretion rate (Green *et al.*, 1988).

### Summary

Taken together, these studies demonstrate that in order to maximize the predictive value of stress-immune function research, experimenters need to include potential moderators and mediators in their study designs. However, integrating and drawing conclusions from these studies is difficult, for a number of reasons, described below.

Sense of humor was one of the most-examined personality variables. While humorous movies were consistently found to induce short-term increases in s-IgA, the results for sense of humor were inconsistent. Individuals who scored high on measures of sense of humor were found to be more responsive to comic material (Lefcourt *et al.*, 1990), less responsive to comic material (Dillon *et al.*, 1985), or responded the same way to comic material as individuals who scored low on sense of humor (Lefcourt *et al.*, 1990). In addition, it is not clear if sense of humor is associated with higher levels of resting levels of s-IgA, since some authors found a positive relation (Dillon *et al.*, 1985), while others reported no relation (Labott *et al.*, 1990; Lefcourt *et al.*, 1990). These contradictory findings may be due to the fact that the studies differed in several key variables, including the measures used to assess sense of humor, movies selected to elicit humor, and methods used to assay s-IgA.

Inhibited power motivation is another personality variable that has been extensively studied. All of these studies were correlational and as such do not address the issue of causality. Importantly, the findings were often inconsistent. Individuals who scored high on inhibition (in combination with need for power and power stress), for example, were reported to have lower levels of s-IgA concentrations in some studies (McClelland *et al.*, 1980), yet higher levels of s-IgA concentrations were observed in other studies (McClelland *et al.*, 1982). Moreover, high levels of affiliative need were found to be associated with higher levels of s-IgA secretion rate during both stress and non-stress periods (Jemmott *et al.*, 1983), but this finding was not replicated for s-IgA concentration (McClelland *et al.*, 1985). Again, these discrepancies may be due to the different subject populations used in these studies as well the different methods used to assay s-IgA.

It is implied in all of these studies that individuals with different personality profiles differ in how they appraise and cope with the stressors they encounter. For example, individuals high in inhibited power motivation are expected to appraise and cope differently than subjects low in need for power. Thus, consistency in coping across different situations and individuals is implied by these authors. However, the efficacy of using personality traits in predicting behavior has been challenged (Michel, 1968, 1973). In general, individuals are characterized more by variability than stability in coping (Folkman and Lazarus, 1980; Lazarus and Folkman, 1984). We found no direct evidence that coping affects or alters the stress-induced changes in s-IgA.

The finding by Jemmott and Magloire (1988) that social support was associated with higher levels of s-IgA is interesting, since several studies have demonstrated that social support is related to health outcomes. However, since this was the only study that examined the role of social support, it is not clear if social support affects s-IgA regardless of whether the individual is undergoing stress or if it also buffers the effects of stress on s-IgA. Clearly, studies are needed that replicate and extend (*i.e.*, manipulate social support) this finding.

## The Mediational Role of Emotional Distress

The above studies lend some support to the hypotheses that stressors and psychobehavioral interventions can affect s-IgA. But how do stressors and psychobehavioral interventions result in s-IgA alteration? One possible pathway is that stressors and interventions affect psychological distress, which in turn affects biological systems (*i.e.*, nervous system, neuroendocrine system) that influence immunologic processes, including s-IgA (see Stone *et al.*, 1996). Several of the studies reviewed above did not include measures of psychological distress and could not address this hypothesis. Those that did either found no changes in psychological distress or did not examine whether changes in psychological distress mediated the changes in s-IgA levels. For example, one study (Rider *et al.*, 1990) found that psychological distress was reduced after a psychobehavioral intervention, and three studies (Jemmott *et al.*, 1983; Mouton *et al.*, 1989; Evans *et al.*, 1994) found that academic examination increased psychological distress. However, since none of these studies examined the relation between changes in psychological distress and changes in s-IgA, there is no evidence that changes in s-IgA observed after various interventions

and stressors are mediated by changes in psychological distress.

The strongest support for the hypothesis that psychological distress mediates the relation between stress and s-IgA comes from Stone *et al.* (1994), described above. A recent analysis of the data from Stone *et al.* (1996) used analyses specifically designed to address third-variable mediational questions. Results indicated that the negative relation between undesirable events and s-IgA antibody production was mediated by increases in negative mood, and the positive relation between desirable and s-IgA antibody production was mediated by increases in positive mood.

Other studies have examined the impact of positive and negative affective states without an explicit stressor. Stone *et al.* (1987a) examined the relation between daily fluctuations in mood and s-IgA antibody production. Throughout an eight-week period, 30 male dental students ingested a daily capsule containing a purified rabbit albumin, and three times a week over the eight-week period they completed the Nowlis Mood Adjective Checklist (Nowlis, 1965) and provided saliva samples that were assayed for IgA antibody production to the albumin. Examination of s-IgA antibody responses showed that antibody response was lower on days with high levels of negative mood relative to days with low levels of negative mood. On the other hand, antibody production was higher on days with high levels of positive mood relative to days with low levels of positive mood. Stone *et al.* (1994) replicated their finding: Positive affect was associated with higher levels of antibody production, and negative mood was associated with lower levels of antibody production. As raised by the authors (Neale and Stone, 1989), one possible explanation for these findings is that negative daily events affect the fluctuation in mood, which in turn suppresses s-IgA antibody production. This is an unlikely explanation, since the authors found, in one of their subsequent studies, that the relationship between s-IgA antibody production and mood remained significant after daily events were controlled for (Stone *et al.*, 1996).

In the Evans *et al.* (1993) study reviewed above, 12 subjects completed the Nowlis Mood Adjective Checklist and provided saliva samples daily for 14 days. No relation was observed between affect (positive and negative) and s-IgA concentration and secretion rate when the data were averaged across all days. On the other hand, within-subject analyses showed that s-IgA concentrations and secretion rates were higher on days with high levels of negative affect. Although not significant, there was a trend for s-IgA concentration and secretion rate to be lower on days with high levels of positive affect.

Using a between-subjects analysis in their study of 114 nurses, Graham and colleagues (1988) found that nurses who reported that they were frequently anxious had lower secretion rates of s-IgA than nurses who reported that they were "occasionally" anxious, but no differences in s-IgA concentrations were observed. Both s-IgA concentration and secretion rate were unrelated to depression, as measured by one item ("How often do you feel depressed?"), and to psychological distress, as measured by the health questionnaire (Goldberg, 1972). It is possible that the anxiety-associated reductions in IgA secretion rates were due to the rate of saliva flow, which is under autonomic control, rather than to direct influence on the s-IgA secretion rate.

In the study by Green and colleagues (1988), reviewed above, no relation was observed between s-IgA concentration and subjective distress as measured with the Hopkins Symptom Checklist (Derogatis *et al.*, 1974). Kugler *et al.* (1992) collected saliva and administered a mood adjective checklist to 84 medical students. Of the 15 dimensions on their adjective checklist, only "excitement" was positively related to s-IgA concentration.

### Summary

Although relatively few studies have examined the relation between subjective distress and s-IgA, the above studies suggest that in order to understand the influence of the psychosocial environment on s-IgA, future researchers should include measures of affect and subjective distress in their study design. The findings by Stone *et al.* (1987a, 1996)—that both negative and positive affects mediated the relation between daily events and s-IgA antibody production—indicate that researchers should not only focus on the role of negative affect but should also consider the contribution of positive affect.

With the exception of the daily assessment studies, the above studies assessed psychological distress or affect at one point in time, and it was not clear what time frame was used. The reliability of subject recall is an issue in those studies that may have used a long time frame.

## *Conclusion and Future Directions*

It is clear that there is substantial evidence that psychosocial variables can affect secretory immunoglobulin A. It should also be evident that it is difficult to compare and draw definite conclusions from these studies, since they differed in several key variables, including the duration and type of the stressors and interventions, timing of assessments relative to the stressors and interventions, and methods used to assay secretory IgA. The majority of the reviewed studies assessed concentrations of s-IgA without controlling for the amount of saliva collected during the sampling period. Therefore, the possibility that the stress-elicited changes in s-IgA concentration were due to stress-induced changes in flow rate cannot be ruled out. Secretory IgA secretion rate was assessed in some of the above studies, and in some

instances, opposite patterns were observed for s-IgA secretion rate and s-IgA concentration. For example, McClelland *et al.* (1985) found that an examination stress increased s-IgA concentration, whereas Jemmott *et al.* (1983) found that the same stressor decreased s-IgA secretion rate. Herbert and Cohen (1993), in their meta-analytic review, compared the results of studies that reported the concentration of s-IgA with those that reported the secretion rate. Their analysis showed that the association between stress and s-IgA concentration was significantly stronger than the association between stress and s-IgA secretion rate. Until more studies have demonstrated that psychosocial factors affect s-IgA after controlling for salivary flow rate, results of s-IgA concentration have to be interpreted cautiously.

Studies that examined the relation between stressful events and s-IgA support the hypothesis that events are associated with reduced s-IgA. However, since all of these studies were correlational, they do not address the issue of causality. The clinical significance of these stress-elicited changes in s-IgA is not yet known, and these alterations may reflect transient fluctuations within the range of normal function. Some investigators assessed whether subjects had been sick in the months preceding their participation in the studies. McClelland and colleagues (1980, 1982) found some evidence that subjects who were high in need for power and high on power-related stress had lower levels of s-IgA concentrations and reported more illnesses in the previous 12 months than other subjects. On the other hand, Graham *et al.* (1988) found no relation between s-IgA secretion rate and upper respiratory infection in the past 12 months. One difficulty with interpreting these findings is that it is not clear if subjects were sick at the time that their saliva was collected for immune assessments, which could affect s-IgA concentrations and secretion rate.

Stone and colleagues found (Stone *et al.*, 1987a, 1994) that stress interfered with the production of antibody responses to a novel antigen. These findings indirectly support the hypothesis that stress-induced changes in s-IgA may have clinical significance, since the responses to the novel antigen may be analogous to those that would occur if the individual were exposed to a virus or a bacterium. Clearly, longitudinal and experimental studies are needed for further examination of the clinical impact of stress-induced changes in s-IgA.

The mechanism whereby stress affects s-IgA is not clear. It has been hypothesized that stress affects the activity of the immune system through its impact on the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Several studies have demonstrated that these pathways are activated by stress, which results in increased levels of circulating catecholamine and cortisol. There is also accumulating evidence indicating that the immune cells have receptors for these hormones, which supports the hypothesis that they are involved in immune modulation (see review by Rabin *et al.*, 1989; O'Leary, 1990; Ader *et al.*, 1991; Ader and Felten, 1995; Weigent and Blalock, 1995; Bedovsky and Rey, 1996). Some of the studies reviewed above did assess catecholamine (McClelland *et al.*, 1985; Kugler *et al.*, 1992, 1993) and cortisol (Evans *et al.*, 1994). Although changes in these hormones were observed in parallel to changes in s-IgA, it is not clear if these hormonal changes accounted for or contributed to the stress-induced changes in s-IgA, since the investigators either found no relation between their hormonal measures and their measurers of s-IgA or did not examine whether the immune changes were due to the hormonal changes. That is, mediational models of the observed relations were not tested. Thus, whether stress affects the activity of s-IgA through its impact on neuroendocrine pathways has not been answered.

There is some evidence that psychological distress mediates the relation between stress and s-IgA. Stone and colleagues (1996) found that increases in negative mood mediated the negative relation between undesirable events and s-IgA antibody production, and that increases in positive mood mediated the positive relation between undesirable events and s-IgA antibody production. It is possible that behavioral responses account for the immune changes found in theses studies. There is evidence that health practices—such as smoking, amount of sleep, and alcohol consumption—can affect the activity of the immune system (MacGregor, 1986; Irvin *et al.*, 1992), including s-IgA (Bennet and Reade, 1982). Until additional studies are conducted that control for these health practices, the possibility that the stress-induced changes in s-IgA were due to changes in health practice cannot be ruled out.

The literature on the effects of psychobehavioral intervention on s-IgA is promising but preliminary. These studies tested various intervention techniques, and short-term increases in s-IgA were observed. It is not clear how long these changes persist, and it is not yet known whether these interventions will buffer the effects of stress on s-IgA, since none of the studies exposed subjects to stress after they had undergone the intervention. The clinical significance of these changes is also not known. The only study that assessed number of symptoms (Rider *et al.*, 1990) found that subjects who were trained in relaxation had higher levels of s-IgA and reported fewer symptoms during the study; however, the particular symptoms affected were not immune-related (breathing difficulty, jaw clenching, and rapid heartbeat).

It is not clear through which mechanism these interventions affected s-IgA. These interventions presumably reduce subjective distress and physiological arousal. Only two studies included neuroendocrine assessments (Green and Green, 1987; Jasnoski and Kugler, 1987), and both studies reported that there was no change in these

measures following the intervention. Surprisingly, of the three studies (Green *et al.*, 1988; Rider *et al.*, 1990; Groer *et al.*, 1994) that assessed psychological distress, only one study (Rider *et al.*, 1990) observed a decrease in psychological distress after the intervention. Systematic investigations of the mechanisms underlying the effects of psychosocial interventions on s-IgA are needed, since those studies will provide information about both the clinical significance of psychosocial interventions and the possible primary and secondary mechanisms underlying the relation between stress and s-IgA.

It is clear that there has been a considerable effort to understand how the psychosocial environment affects s-IgA. While the majority of studies support an association, several issues concerning this literature remain problematic and should be the object of future research. Results are not consistent among studies using s-IgA concentration and secretion rates as outcomes. The resolution of these issues may lie in the proper measurements of salivary flow. Questions have been raised about the meaning of total s-IgA assessments, and empirical work is needed for the health consequences of total and/or specific measures of s-IgA to be shown convincingly. Psychologic and physiologic pathways translating environmental events into changes in s-IgA also need to be systematically investigated.

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# Predictors of intrusive thoughts and avoidance in women with family histories of breast cancer.

Sandra G. Zakowski, Ph.D.[1], Heiddis B. Valdimarsdottir, Ph.D.[1], Dana H. Bovbjerg, Ph.D.[1], Patrick Borgen, M.D.[1], Jimmie Holland, M.D.[1], Kathryn Kash, Ph.D.[1,2], Daniel Miller, M.D.[2], Julie Mitnick, M.D.[3], Michael Osborne, M.D.[2], Kimberly Van Zee, M.D.[1].

[1] Memorial Sloan-Kettering Cancer Center, New York, NY, USA

[2] Strang Cancer Prevention Center, New York, NY, USA

[3] Murray Hill Radiology and Mammography, New York, NY, USA

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Author to whom correspondance should be addressed: Sandra G. Zakowski, Ph.D., MSKCC, Box 457, 1275 York Ave., New York, NY 10021.

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## Abstract

Having a family history of cancer is an important predictor of lifetime cancer risk. Individuals with family histories of cancer have been reported to experience symptoms of general distress and to have frequent intrusive thoughts and avoidance regarding cancer. To date, little is known about predictors of such distress. A relation between perception of cancer risk and distress has been suggested, but the possibility that prior cancer-related events may contribute to distress in these women has received little attention. The major aim of the study was to examine the contribution of the past experience of the death of a parent from cancer to distress in women at familial risk for breast cancer.

Women with family histories of breast cancer (Risk Group, n=46) were assessed on the day of their yearly mammography screening and four to eight weeks after normal result notification, in order to confirm the generalizability of their distress. Their levels of intrusive thoughts, avoidance, and perceived lifetime risk for breast cancer were significantly higher than those of women with no family histories of cancer who were not undergoing mammography (Comparison Group, n=43), and this was true on both assessment days. Among the women in the Risk Group, those whose parent(s) had died of cancer had the highest levels of intrusive thoughts, avoidance and perceived risk. Results suggested that perceived risk mediated the effect of this event on intrusive thoughts and avoidance regarding breast cancer. The findings are discussed in terms of theories of cognitive responses to traumatic and stressful life events. Implications for future research and interventions are discussed.

## Introduction

Having a family history of cancer is a significant risk factor for developing cancer in one's lifetime (1). Several recent studies, although not all (2), have shown that having a family history of cancer including breast cancer may be associated with elevated levels of distress (3-5). For example, Valdimarsdottir et al. (5) compared women with and without family histories of breast cancer. Those who had family histories of breast cancer had significantly higher levels of intrusive thoughts and avoidance on the Impact of Events Scale (IES, (6)), as well as higher levels of general distress, anxiety, phobic anxiety, somatization, and depression on the Brief Symptom Inventory (BSI). Kash et al. (3) found that 27% of women with family histories of breast cancer endorsed levels of distress on the BSI that suggested a need for psychological counselling. In a study by Lerman et al. (4) women with family histories of breast cancer reported levels of intrusive thoughts that were comparable to those found in clinical populations. In 30% of these women, worries about breast cancer interfered with their daily lives. Preliminary data also suggested that women with family histories of cancer may have mood disturbances comparable to those seen in patients recently diagnosed with breast cancer (7).

Despite the accumulating evidence that women with family histories of cancer have higher levels of distress, it is clear that not all of these women are equally affected. While some women may have reactions severe enough to warrant clinical attention (3,4) others have less severe stress symptoms. To date, little is known about the predictors of distress in women with family histories of cancer, as only a few studies have addressed this issue. Schwartz et al. (8) showed a relation between perceived risk for cancer and intrusive thoughts as well as an indirect relation between a monitoring coping style and intrusive thoughts. Lerman, Kash, and Stefanek (9) suggested that a woman's current age may be associated with her levels of distress. Wellish et al. (10) reported that a woman's age at the time of her mother's breast cancer diagnosis was associated with distress levels in that those who were adolescents at the time appeared to have the greatest adjustment problems.

Yet to be considered is the impact of past cancer-related events, chief among which is likely to be a parent's death from cancer. The loss of a parent from cancer, which may be

preceded by a long and painful decline in the parent's health, and which can entail longterm care-giving needs provided by close family members, is an event that seems likely to contribute to chronic stress especially when the bereaved perceive themselves at risk for the disease and may live in fear of meeting the same fate. Consistent with this hypothesis, research on the psychological effects of experiencing the death of a parent to any cause has shown that this life event has profound psychological consequences including distress, intrusive thoughts and avoidance (11-16). In addition to symptoms of distress, a feeling of vulnerability (or perceived risk) which may be triggered by stressful or traumatic events including a parent's death (16,17), is an important response to take into consideration as it appears to play an important role in women with family histories of cancer (18). Perceived risk for developing cancer has been shown to be associated with distress in these women (8).

The principal aim of the present longitudinal study was to examine the contribution of a past experience of parental loss to cancer to distress in women who are at familial risk for breast cancer. To address this aim, we first sought to replicate previous findings by Valdimarsdottir et al. (5), which indicated that women with family histories of breast cancer have higher levels of distress, including intrusive thoughts and avoidance about breast cancer as well as more general distress compared to women without cancer in their families. Since that study and others have shown that distress about cancer may be more prominent in women with family histories of cancer when specific cancer cues (e.g., mammography) are present (5,19) we assessed distress twice in this group, once on a day of mammography and once four to eight weeks after notification of normal mammography results. As in our previous study (5), women without family histories of cancer were concurrently assessed on two occasions without mammography, to provide an indication of distress levels in the community and to control for the effects of two assessments per se. We then extended the previous findings by examining the contribution of having experienced a parent's death from cancer to the elevated levels of distress (general distress as well as intrusive thoughts and avoidance regarding breast cancer) and perceived risk reported by women with family histories of breast cancer. For this purpose, women with family histories of breast cancer were divided into two subgroups: those whose parent(s) had died from cancer and those whose

parents had not died from cancer. These subgroups were then compared to the group of women without family histories of cancer. Finally, among the women with family histories of cancer, we then further explored predictors of their distress. Based on previous research on bereaved individuals, as well as women at risk for cancer (8,16), we hypothesized that a greater sense of personal vulnerability to developing breast cancer (i.e., perceived risk) in the women whose parent(s) had died of cancer may account for the higher levels of distress in these women. Our repeated measures design allowed us to explore whether these relations were more prominent on a day when cancer-related cues are present (Assessment Day 1) compared to a day without such a cue, four to eight weeks after receiving the news of normal mammography results (Assessment Day 2).

## Method

### Subjects

The study included a total of 89 women who were participating in a broader longitudinal study examining the psychobiological effects of mammography screening in women at familial risk for breast cancer. All subjects who were recruited since we revised our family history questionnaire to obtain data necessary to address the present hypotheses (e.g., cause of parent's death) were included in this study. Of those, 46 women with at least one first degree relative (mother, sister, daughter) who had previously been diagnosed with breast cancer (Risk Group), were recruited from three cancer screening programs in New York City prior to a routine mammography screening. The remaining 43 women had no cancer history in their first degree relatives (Comparison Group) and were recruited through advertisements in the community[1]. Eligible subjects had no personal history of neoplasm or chronic disease, no prior abnormal mammograms or biopsies, no current chronic mental or physical illness, and were not taking medication on a regular basis. Women whose first-degree relatives were currently under active cancer treatment were excluded from the study. Subjects' ages ranged from 22.8 to 54.6 ($M$=41.6, $SD$=6.8), the majority of subjects were Caucasian, married, employed, and had at least some college education.

For some of the analyses, subjects in the Risk Group were split into two subgroups based on whether or not they had experienced the death of a parent from cancer. Risk Subgroup 1 consisted of the subjects who had at least one parent who had died of cancer (n=30; mother died: n=18, father died: n=5, both parents died: n=7) and Risk Subgroup 2 included those whose parents had not died of cancer (n=16). The cause of death of all the deceased mothers in Risk Subgroup 1 was breast cancer. It should be noted that some of the women in the Risk Group had more than one first degree relative who was diagnosed with cancer. This variable (number of first degree relatives with cancer) was therefore included in the initial statistical analyses assessing subgroup comparability.

Procedures

Women with family histories of breast cancer (Risk Group) were recruited by telephone approximately one week before a scheduled routine mammography screening for breast cancer. They were first assessed in the clinic prior to mammography (Assessment Day 1) and then assessed again four to eight weeks later (Assessment Day 2). On Assessment Day 1, subjects completed several questionnaires including a family history questionnaire, demographics, a perceived risk scale, the Brief Symptom Inventory (BSI; (20)) assessing general distress, and the Impact of Events Scale (IES; (6)) assessing intrusive thoughts and avoidance regarding breast cancer. They also underwent mammography screening and were informed of their results[1]. None of the women had abnormal mammography results. On Assessment Day 2, subjects again completed the BSI, the IES, and the perceived risk scale in the absence of mammography screening. Women without family histories of breast cancer (Comparison Group) were scheduled for concurrent research assessments with the Risk Group but were not scheduled for mammography. This Group was included in this study in order to provide comparison data from a healthy community sample that had not experienced cancer in first-degree relatives allowing us to control for the stress of daily living in an urban community and to examine the effects of two assessments per se.

Measures

Demographic questionnaire. Subjects completed a standard questionnaire asking about their age, race, education, income, and marital status (5).

Family History of Cancer. This questionnaire was designed to assess the occurrence of cancer in subjects' biological relatives as well as other variables related to the cancer diagnosis, including age of the patient at time of diagnosis, survival status, and age of the subject at the time of the relatives' diagnosis and death (if applicable). Lifetime objective risk was calculated based on the Claus and the Gail models (21,22). Both models were included in this study because they use different variables to calculate risk (and often yield different risk scores) and have both been used in previous studies of breast cancer risk (1). The Claus model takes into account the number of affected first and second degree relatives, and age of relatives at time of diagnosis (22). The Gail model takes into account the number of affected first degree relatives, age at first live birth, age of menarche, number of benign breast biopsies, and history of breast biopsies with hyperplasia (21).

Perceived risk for breast cancer. Subjects rated their perceived likelihood of developing breast cancer in their lifetime from 0 (not at all likely) to 100 (extremely likely) (5). This measure was administered at both assessment days. Because results from the two Assessment Days were highly correlated ($r=.85$, $p<.0001$) and the perceived risk scores obtained at the two assessments did not differ significantly, the combined mean of the two scores was used for subsequent statistical analyses.

Brief Symptom Inventory (BSI; (20)). The BSI was administered on both assessment days as a measure of general distress. The BSI includes nine subscales based on separate symptom dimensions (somatization, obsessive compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and one general score, the General Severity Index (GSI). The BSI was selected because it has been used in previous studies of distress in women at familial risk for breast cancer (3,5). Subjects indicated on a scale from 0 (not at all) to 4 (extremely) how much discomfort each of the symptoms had caused them "in the past week including today".

Impact of Events Scale (IES;(6)). This questionnaire assesses the frequency of intrusive

thoughts and avoidance with regard to a specific stressor. The specific stressor chosen for the IES was breast cancer. The IES consists of 15 items, including seven items for the intrusion subscale and 8 items for the avoidance subscale. This measure was chosen because it assesses symptoms reflective of current distress (6), and because it has been used in studies of responses to parental death (13) as well as studies of cancer-specific distress in women at familial risk for cancer (5,8). Subjects were asked to rate how frequently each thought or behavior occurred "during the past week including today".

Statistical analyses

Analyses of Variance (ANOVA) and Chi-Square analyses were first conducted to test possible group differences in demographic variables. Any variable that was found to differ among the groups and was correlated ($p < .1$) with the dependent variables was included as a covariate in subsequent analyses. Repeated measures ANCOVA was then used to examine differences between the Risk Group and the Comparison Group in distress (BSI, IES) on the two Assessment Days, and in perceived risk. In the second phase of the analysis, the Risk Group was divided into two Risk Subgroups according to the women's experience of a parental death from cancer. In addition to assessing general demographic variables, we also examined factors associated with the cancer diagnosis in the two Risk Subgroups[2], including the number of affected first degree relatives, their age at time of diagnosis, the subject's age then, the recency of diagnosis, and subject's objective risk (Claus and Gail models). We applied the same rule for including covariates as we did in the analyses described above. A similar repeated measures ANCOVA then compared these two Risk Subgroups with the Comparison Group on the same dependent measures. Post-hoc analyses were done using the Duncan test with an alpha level set at .05. The third phase of the analysis consisted of a series of regression analyses examining the possible role of perceived risk as a mediator of the associations between the Risk Subgroups and intrusive thoughts and avoidance. Whenever there was no significant Assessment Day by Group interaction, Beta weights and $r^2$ values were calculated using the mean of IES scores across the two Assessment Days in regression analyses.

Finally, additional analyses were conducted to examine potential associations of variables

related to the parent's cancer death with the subject's distress and perceived risk. This was done to explore possible mechanisms for the association between the experience of a parent's death from cancer and distress in order to provide suggestions for future research.

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Insert Tables 1 and 2 about here

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## Results

### Group and Subgroup comparability

The Risk and Comparsion Groups were significantly different on two of the demographic variables, marital status and subject's current age, $X^2(88)=12.15$, $p<.001$, and $F(1,87)= 5.12$, $p<.03$, respectively (see Table 1). Since these variables were significantly related with distress and perceived risk ($p<.1$) we included age and marital status as covariates in all the analyses comparing the Risk Group with the Comparsion Group. No significant differences were seen for any other demographic variables.

We also compared demographic and diagnosis-related variables between the two Risk Subgroups. There was a significant difference for the subject's current age, for recency of the affected relatives' diagnosis, and subject's age at the time of diagnosis, $F(1,45)=9.36$, $p<.01$; $F(1,44)=17.14$, $p<.01$; $F(1,44)=3.99$, $p=.05$, repectively (see Table 2). In addition, there was a marginally significant difference for the number of first degree relatives diagnosed with cancer, $X^2(45)=3.49$, $p=.062$, (see Table 2). As none of these variables were significantly related to the distress or perceived risk measures in the two Risk Subgroups (all p's>.2) they were not included as covariates inthe analyses. No significant differences were seen for any other demographic or diagnosis-related variables.

### Effects of family history of breast cancer on general distress, intrusive thoughts and avoidance, and perceived risk

First, we sought to confirm that having a family history of breast cancer was associated

with higher levels of general distress (BSI), intrusive thoughts and avoidance about breast cancer, and perceived risk. Unlike our previous report (5), repeated measures analysis of covariance using the general severity index (GSI) of the BSI as a dependent variable, yielded no significant difference between the groups on this measure of general distress.

Repeated measures ANCOVA using IES scores on the two Assessment Days yielded a significant Group main effect, $F(1,85)=12.45$, $p<.001$. Post-hoc analyses showed that the Risk Group had significantly higher levels than did the Comparison Group on both Assessment Days (Duncan, $p<.05$). No significant interaction effects by Assessment Day were found, suggesting that differences in IES scores remained elevated in the Risk Group regardless of the presence or absence of the cancer-related cue. In addition, there were no significant interactions by IES subscales, suggesting that intrusive thoughts and avoidance showed the same patterns of differences between the groups.

Finally, the Risk Group also had higher perceived risk scores than did the Comparsion Group as shown by a significant main effect, $F(1,85)=28.14$, $p<.0001$ (Risk Group: $M=64.19$, $SD=23.61$; Comparison Group: $M=31.99$, $SD=22.02$).

Effects of experiencing the death of a parent from cancer on general distress, intrusive thoughts and avoidance

To allow examination of the contribution of having experienced the death of a parent from cancer to these women's levels of distress and perceived risk, the Risk Group was split into the two subgroups. Repeated measures ANCOVA comparing GSI scores across the three groups (the Comparison Group and Risk Subgroups 1 and 2) again revealed no significant differences, suggesting that the three groups were similar on this measure of general distress.

Analyses on the IES yielded a significant main effect of Group, $F(2,84)=9.69$, $p<.001$ when marital status and age were controlled (see Figure 1). There was no significant main effect of Assessment Day, no Group by Day interaction, and no significant interactions by IES subscales. Post-hoc analyses showed that women at familial risk who had experienced the death of a parent from cancer (Risk Subgroup 1) had the highest intrusive thoughts and avoidance regarding breast cancer across assessment days, whereas those women at familial risk whose

parents had not died from cancer (Risk Subgroup 2) were statistically comparable to normal risk women (Duncan, $p<.05$). This is consistent with the idea that the heightened intrusive thoughts and avoidance in women at familial risk can, at least in part, be explained by their experience of parental death from cancer.

Insert Figure 1 About Here

Death of a parent from cancer and perceived risk

In order to examine the contribution of the death of a parent from cancer on subjects' levels of perceived risk for breast cancer, we conducted an ANCOVA comparing the two Risk Subgroups to the Comparison Group on this variable. Results showed a significant main effect for Group, $F(2,84)=17.98$, $p<.001$, after marital status and age were covaried. As expected, Risk Subgroup 1, whose parent(s) had died of cancer, reported significantly higher levels of perceived risk than the other two groups, whereas the Comparison Group had the lowest scores on this measure (Risk Subgroup 1: $M=70.35$, $SD=23.71$; Risk Subgroup 2: $M=52.66$, $SD=19.20$; Comparsion Group:$M=32.00$, $SD=22.02$). All three groups were significantly different from one another (Duncan, $p<.05$).

Perceived risk, intrusive thoughts and avoidance

Among the women with family histories of breast cancer, those whose parent(s) had died of cancer had higher levels of intrusive thoughts and avoidance as well as higher perceived risk than those whose parent(s) had not died of cancer. It was therefore of interest to examine the possibility that perceived risk might mediate the relations between the experience of a death of a parent from cancer and intrusive thoughts and avoidance.

In accordance with the conceptualization of mediation described by Baron & Kenny (24), we first ascertained the effects of Risk Subgroups on the IES and perceived risk scores omitting the Comparison Group from the analyses. Risk Subgroup 1 was significantly higher on both, IES scores, $F(1,44)=5.40$, $p<.03$, ($r^2=.11$, $B=.33$), and perceived risk, $F(1,44)=6.58$, $p<.02$, ($r^2=.13$,

B=.36). We then used regression analyses to test the possible mediating effect. First, we examined whether the hypothesized mediator (perceived risk) predicted the dependent variable (IES scores at the two assessment days) using a repeated measures regression equation. Perceived risk was a significant predictor of IES scores on both Assessment Days as shown by a significant main effect, $F(1,44)=11.54$, $p<.002$, ($r^2=.21$, $B=.46$) and no significant interactions. The results suggest that high perceived risk scores predict high levels of intrusive thoughts and avoidance regarding breast cancer.

Second, if perceived risk acts as a mediator of the differences between the Risk Subgroups on IES scores, then the effect of Risk Subgroup on IES scores should be reduced or eliminated when perceived risk is statistically controlled (24). Perceived risk and Risk Subgroup variables were entered consecutively into a repeated measures multiple regression correlation which yielded a significant main effect for perceived risk on the IES, $F(1,43)=7.34$, $p<.01$, and a nonsignificant effect for Risk Subgroup, $F(1,43)=1.80$, $p>.18$ ($r^2= .03$, $B=.19$) (see Figure 2). When the IES was broken down into its subscales of intrusive thoughts and avoidance, analyses yielded no Subscale by Risk Subgroup interactions. These results suggest that perceived risk significantly mediated the subgroup difference in the levels of intrusive thoughts and avoidance regarding breast cancer. The absence of a significant interaction by Assessment Day indicates that this mediating effect holds irrespective of the presence or absence of mammography screening.

We also examined the possibility that the women's objective risk for breast cancer may significantly contribute to this mediating effect. We found a significant correlation between perceived risk and objective risk scores calculated according to the Claus Model (22), $r=0.34$, $p<.02$. However, there was no significant correlation with objective risk according to the Gail Model (21), nor was there a significant difference among the Risk Subgroups on objective risk for either model (see Table 2). There was also no correlation between either model of objective risk and IES scores. Finally, we examined whether objective risk may account for the relation between perceived risk and IES scores. For this purpose, we included objective risk scores from each model as covariates in a regression equation using perceived risk as a predictor of IES scores and found no change in the significant relation between perceived risk and IES. From this, we can conclude that the mediating effect of perceived risk described above was not confounded by the

women's objective risk for breast cancer.

Insert Figure 2 and Table 2 About Here

Additional analyses on factors related to cancer death of the parent on IES scores and perceived risk

In addition to the main analyses regarding the relations between the parent's death from cancer on perceived risk and distress, we conducted some exploratory analyses examining variables related to the parent's death that were available to us in order to further characterize distress related to this potentially traumatic event. These included age of the subjects at the time the parent died, age of the parent then, and recency of the parent's death[2] (see Table 2). None of these characteristics showed significant associations with IES scores regarding breast cancer or perceived risk for breast cancer in these women.

## Discussion

The main goal of the present study was to examine the contribution of having experienced the death of a parent from cancer to current intrusive thoughts, avoidance, and perceived risk regarding breast cancer in women at familial risk for this disease. In order to address this aim, we first sought to replicate previous findings that women with family histories of breast cancer have more distress, in the presence or absence of a cancer related cue, than women without such family histories (5). These variables were assessed in women at familial risk for cancer on two separate occasions, on a day of routine mammography screening (Assessment Day 1) and on a day with no explicit cancer-related stressor (Assessment Day 2) four to eight weeks after notification of normal mammography results. The Risk Group had significantly higher levels of intrusive thoughts and avoidance regarding breast cancer than did the Comparison Group which confirmed the previous report by Valdimarsdottir et al. (5). This was true on the day of mammography and

one to two months later. However, unlike that previous study which found women with family histories of breast cancer to have higher general distress (GSI) on the BSI, we found no differences between the groups on that measure. Differences in recruitment strategies may account for the higher distress found in the former study, because Valdimarsdottir et al. (5) recruited women from a high risk clinic, whereas we recruited women through three different mammography screening programs not exclusively targetted to women at high risk for breast cancer. The heightened levels of cancer-specific intrusive thoughts and avoidance, which have been reported in several studies (4,5), may be the predominant symptoms of distress in these women. Intrusive thoughts and avoidance have also been associated with lower levels of adherence to mammography screening (3,4) which underscores the importance of examining the sources of these symptoms more closely.

Further, women in the Risk Group had significantly higher levels of perceived risk for breast cancer than women in the Comparison Group. Previous studies have shown that women with family histories of cancer estimate their own risk to be high. For example, Valdimarsdottir et al.(5) reported women with family histories of breast cancer to have similar levels of perceived risk as the women in our study (i.e., $\underline{M}$=59.2) and these levels were significantly higher in these women than those reported by the comparison group. Other studies have reported high levels of perceived risk using slightly different measures (3,4), however, none of these studies included a comparison group. It is of interest in the present study that perceived risk was significantly positively correlated with objective risk calculated according to the Claus model but not to the Gail model. The two models use different variables to calculate the risk estimates which often vary based upon which model was used. The Claus model relies more heavily on family history of cancer, whereas the Gail model includes the person's past medical history (see Measures). It is conceivable, that women are more aware of their risk contribution based on family history than on personal medical variables. This may partly be due to media attention devoted to the genetic risk factors of breast cancer. This could be the reason why only the Claus figures were correlated with perceived risk in these women. Only one other study has reported a correlation between perceived risk and objective risk factors (8), however, in that case the correlation was negative. Several differences between that study and the present one may account for this difference in

finding, including the use of different objective and subjective risk measures. It should be noted that the lack of uniformity of subjective and objective risk assessments makes comparisons across studies often difficult, and the standardization of this important measure needs to be addressed in future research.

Having established the higher levels of distress and perceived risk in this sample of women, our main goal was to examine whether having experienced the death of a parent from cancer may contribute to the individual variability in some of these symptoms. The present data suggest this to be the case for intrusive thoughts and avoidance regarding breast cancer. While the two Risk Subgroups did not differ on general distress (BSI), the women whose parent(s) had died of cancer had significantly higher scores on the IES than women in the Risk Subgroup who had not experienced this life event or women in the Comparison Group. There was no significant difference in IES scores between the Risk Subgroup who did not experience a parent's death of cancer and the Comparison Group. While several studies have found that women with family histories of breast cancer have elevated levels of intrusive thoughts and avoidance regarding cancer, the issue of why these symptoms occur has rarely been addressed. Our data suggest that past cancer-related events may be strong determinants of later distress and that having experienced a parent's death from cancer may be a potent stressor that may make the threat of breast cancer especially salient for these women. It is tempting to speculate that, the experience of the parent's death from cancer, in addition to their diagnosis which all the women in our risk group had experienced, may change the meaning of cancer from a potentially curable illness to a death threat. This may heighten these women's distress about cancer in general. However, the death of the parent from cancer does not account for all of the variance in intrusive thoughts and avoidance about breast cancer, suggesting that other predictors also need to be explored.

The fact that the women's perceived risk for breast cancer was affected by the experience of a parental death from cancer may be interpreted in accordance with theories proposed by Janoff-Bulman (17). This author has suggested that traumatic or stressful life events (such as the death of a parent) may challenge one's personal assumptions of invulnerability to harm and injury. While the majority of people tend to have a rather unrealistic sense of invulnerability, that is, they believe the likelihood of "bad things" happening to them to be very low (25), a traumatic event

(e.g., the death of a parent from cancer) may challenge these assumptions. It has been suggested that the change in assumptions about one's personal vulnerability may be specific to the type of event of which the individual was a victim (e.g., children whose parents divorced have more negative assumptions specifically about marriage, not about the world in general (26)). In the present study we found that women whose parent(s) had died of cancer felt more vulnerable to developing breast cancer. The specificity of increased perceived vulnerability will be an interesting question to explore in future studies.

The third aim of the study was to examine the role of perceived risk as a potential mediator for the association between a parent's death from cancer and intrusive thoughts and avoidance concerning breast cancer in women with family histories of breast cancer. Results were consistent with this possibility. Women who had experienced the death of a parent from cancer had the highest levels of perceived risk which in turn accounted for much of their heightened levels of intrusive thoughts and avoidance. Although we found no selective effects of intrusive thoughts vs. avoidance, our results are consistent with the theories put forth by Janoff-Bulman and Horowitz (17,27,28). The discrepancies between one's previous assumptions of invulnerability and the new feeling of vulnerability conveyed by the death of a parent or other events, are thought to create a conflict that may gradually be resolved by intrusive thoughts and avoidance. In theory, these coping processes may be used until reintegration of the new information and the person's existing mental models and world assumptions is achieved and cognitive harmony is restored (27). Our data are in support of this model. Intrusive thoughts and avoidance scores were highly correlated in this study and it appears from the lack of significant interactions by IES subscales, that these coping processes may be affected similarly by the predictors.

It should be noted with regard to these findings that, given that the aim of the study was to assess cancer related distress, we chose to measure intrusive thoughts and avoidance about breast cancer. Had we focused the IES on the death of the parent specifically it is likely that the mediating role of perceived risk between the effect of parental death and IES scores would not have been as strong. It is also interesting that in this study, recency of parental loss (ranging from 1 to 43 years) to cancer was not associated with higher levels of intrusive thoughts and avoidance

or perceived risk. Again, had we focused the IES on the death of the parent from cancer we may well have obtained the expected relation. Finally, we did not find any associations between other diagnosis-related variables such as number of affected first degree relatives, time since their cancer diagnosis and subjects' distress levels. The relations between specific characteristics of a woman's past experience with family history of cancer and her levels of distress should be addressed more systematically in future studies.

Another hypothesis dealt with the effects of a cancer-specific cue in this study. Previous research has suggested that individuals who have experienced stressful events such as bereavement or separation may be more sensitive to cues associated with that event (34). Based on those findings, we expected that women at familial risk who had experienced the death of a parent from cancer would show a greater increase in intrusive thoughts and avoidance, at the time of mammography screening than women who did not have the experience of parental death from cancer. However, the absence of a statistically significant interaction did not support this idea. That is, women in Risk Subgroup 1 had significantly higher scores on the IES independent of this cancer-specific stressor (mammography). It is possible that mammography may not present a cue specific to memories or distressing thoughts related to the parent's death from cancer. Mammography, which is a diagnostic procedure, may be a more specific cue for triggering memories of the parent's diagnosis of breast cancer, an event which all the women in the Risk Group had experienced. Explanations of this effect can, however, merely be speculative at this point.

Several limitations of this study provide suggestions for future research in this area. The sample size in our study did not allow us to conduct more fine-grained analyses of parental death as a life-event. For example, we were not able to compare women whose parent(s) died of cancer with those whose parent(s) died of other causes because there were too few subjects in the latter category. In addition, our relatively small sample size did not allow us to conduct analyses by gender of the deceased parent. Horowitz et al. (13) found that maternal death was associated with more depression and intrusive symptoms than paternal death. Future studies with larger sample sizes may be able to confirm these findings, which may be especially important in women at risk for breast cancer. Further, we were not able to assess the differential impact of having had

one versus two parents die of cancer or that of having a second parent who died of causes other than cancer. These are interesting questions that should be explored in future studies in this population. In addition, further research should be conducted to study the contribution of other dispositional factors that may increase or reduce women's vulnerability to developing stress symptoms.

It could be argued that the women in our Risk Group may not be representative of the general population of women at familial risk because they were participating in mammography screening programs. However, based on the literature suggesting that women who are less distressed are more likely to comply with mammography screening guidelines (3,4) we may expect our data to underestimate the levels of distress that may be found in this population. Future studies should address this issue by including women at familial risk who do not attend such screening programs.

As our comparison group we chose women without family histories of breast cancer who were not undergoing mammography screening at the time of data collection. This enabled us to control for the day-to-day distress in women with similar demographic characteristics living in the same urban community. This is an important control that has only rarely been used in the study of women at familial risk for cancer. It did not, however, allow us to separate the effects of distress due to mammography vs. that of having a family history of breast cancer on Assessment Day 1. The finding that intrusive thoughts and avoidance about breast cancer remained elevated in the Risk Group on Assessment Day 2 (a non-mammography day) suggests that distress in these women may be primarily due to their family history. This should be addressed in future studies including a comparison group of normal risk women from the community who are currently undergoing mammography screening.

The present study on women with family histories of breast cancer is one of the few to incorporate any type of comparison group or to use a longitudinal design. The study not only confirmed previously reported findings that women with family histories of breast cancer have higher levels of intrusive thoughts and avoidance about cancer, but also identified an objective discrete event (the death of a parent from cancer) as a possible contributing source of these symptoms. In fact, our data suggest that only those women at familial risk whose parent(s) had

died of cancer reported significantly higher levels of intrusive thoughts and avoidance than the comparison group, suggesting that parental death may be an important issue to address in future studies of this population. These findings also put into question the potential importance of other current or past cancer-related events that these women may experience, such as caregiving for a parent with cancer, illness of friends and more remote relatives, etc. In addition, having a parent who is currently under active treatment for cancer may be a significant stressor for these women that should be taken into account. With few exceptions (5) most of the studies of women at familial risk for cancer do not explicitely exclude those cases. In fact, women with family histories of cancer are often times recruited through their family members who are currently undergoing treatment for cancer (4,8). Future studies should include current treatment of the family member as a potential additional life stressor that may contribute to these women's distress.

The findings from the present study may have implications for intervention strategies. Recent studies (35,36) have shown that breast cancer risk counselling is effective in helping women with family histories of breast cancer gain a better understanding of their personal risk for breast cancer and in reducing their cancer-specific distress (IES). Another study examining the effects of problem solving training reported that those women who practiced problem solving strategies regularly had reduced cancer-specific distress on the IES (37). Our data suggest that there may be subgroups of women who may be especially prone to distress regarding breast cancer, and that it will be useful to identify those women whose parents had died of cancer as they may be in particular need of counselling. In addition, exploring past cancer-related events as possible sources of these women's distress may prove beneficial in helping women reduce their distress. Specifically, counsellors could address women's reactions to a parent's death from cancer and examine its impact on distress and their exaggerated perceived risk for developing breast cancer. Our data also indicate that the women's high perceived risk may be an important mediator between their experience of a parent's death from cancer and distress. If women's risk perceptions can be rectified to more closely approximate their actual objective risk, it may help to reduce their distress. Finally, cognitive-behavioral strategies may be useful in helping women reduce their distress about breast cancer, to cope with cancer-related events such as deaths in

family members, and to identify and utilize effective coping and screening behaviors.

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**Table 1: Demographic characteristics of subject population:**

| | Risk Subgroup 1 | Risk Subgroup 2 | Comparison Group |
|---|---|---|---|
| Age (years) | 45.0 (4.6) [a] | 40.6 (4.8) [b] | 39.7 (9.9) [b] |
| Education (college grad) | 76.7% [a] | 81.3% [a] | 81.4% [a] |
| Ethnic group (White) | 93.3% [a] | 87.5% [a] | 72.1% [a] |
| Marital status (married) | 76.7% [a] | 62.5% [ab] | 34.9% [b] |

Groups with same superscript are not significantly different ($p > .10$).

**Table 2: Cancer-related variables and objective risk for breast cancer**

| | **Risk Subgroup 1** Mean (SD), Range | **Risk Subgroup 2** Mean (SD), Range |
|---|---|---|
| **Objective risk for breast cancer:** | | |
| - Claus Model | 20.9 (10.5)[a], 8.8-46.0 | 18.2 ( 8.0)[a], 8.8-35.4 |
| - Gail Model | 17.2 ( 4.3)[a], 12.0-31.4 | 18.4 ( 4.5)[a], 15.0-27.8 |
| **Subjects with more than 1 affected first degree relative:** | 46.7% [a] | 18.8% [b] |
| **Cancer diagnosis:** | | |
| - Patient's age then | 53.0 (12.8)[a], 33.0-81.0 | 51.2 (12.6)[a], 33.0-72.0 |
| - Subject's age then | 24.2 (11.9)[a], 1.0-48.0 | 31.0 ( 7.6)[b], 16.0-43.0 |
| - Years since diagnosis | 20.8 ( 9.7)[a], 5.4-42.8 | 9.4 ( 6.1)[b], 1.0-21.6 |
| **Death from Cancer:** | | |
| - Parent's age then | 62.4 (14.7), 35.0-83.5 | n/a |
| - Subject's age then | 31.2 (13.9), 3.0-52.0 | n/a |
| - Years since death | 14.0 (11.3), 1.5-42.8 | n/a |

Groups with same superscript are not significantly different ($p > .1$)

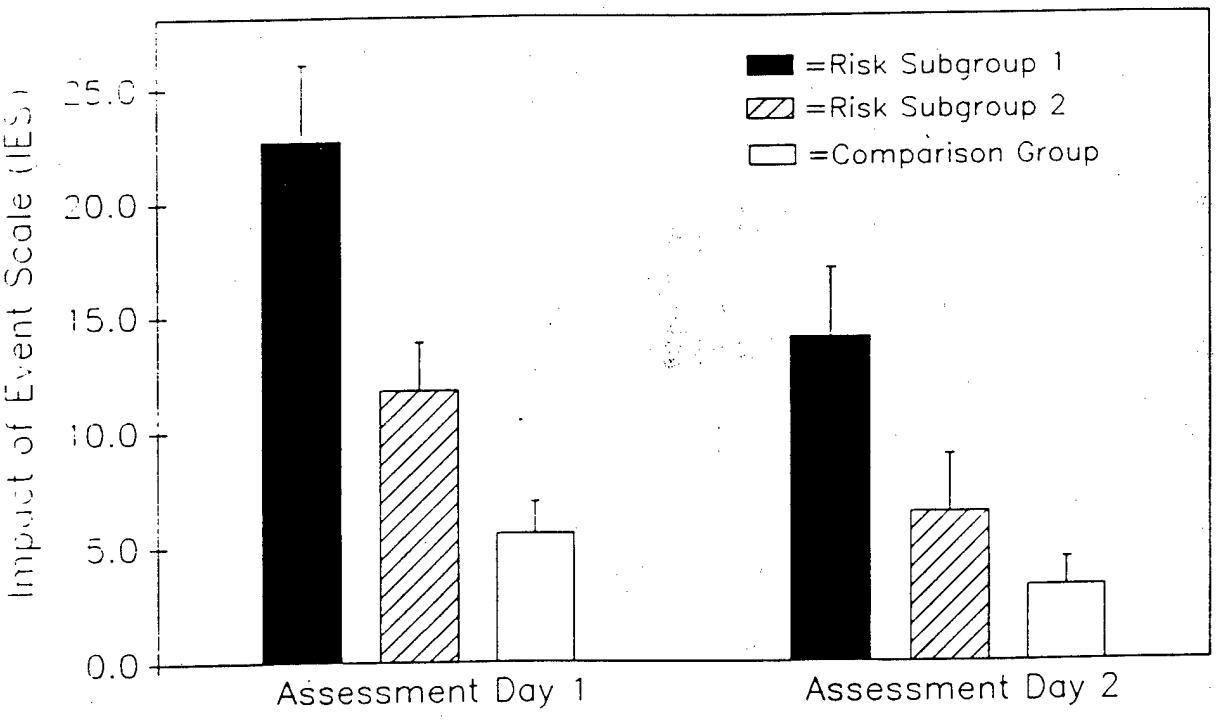
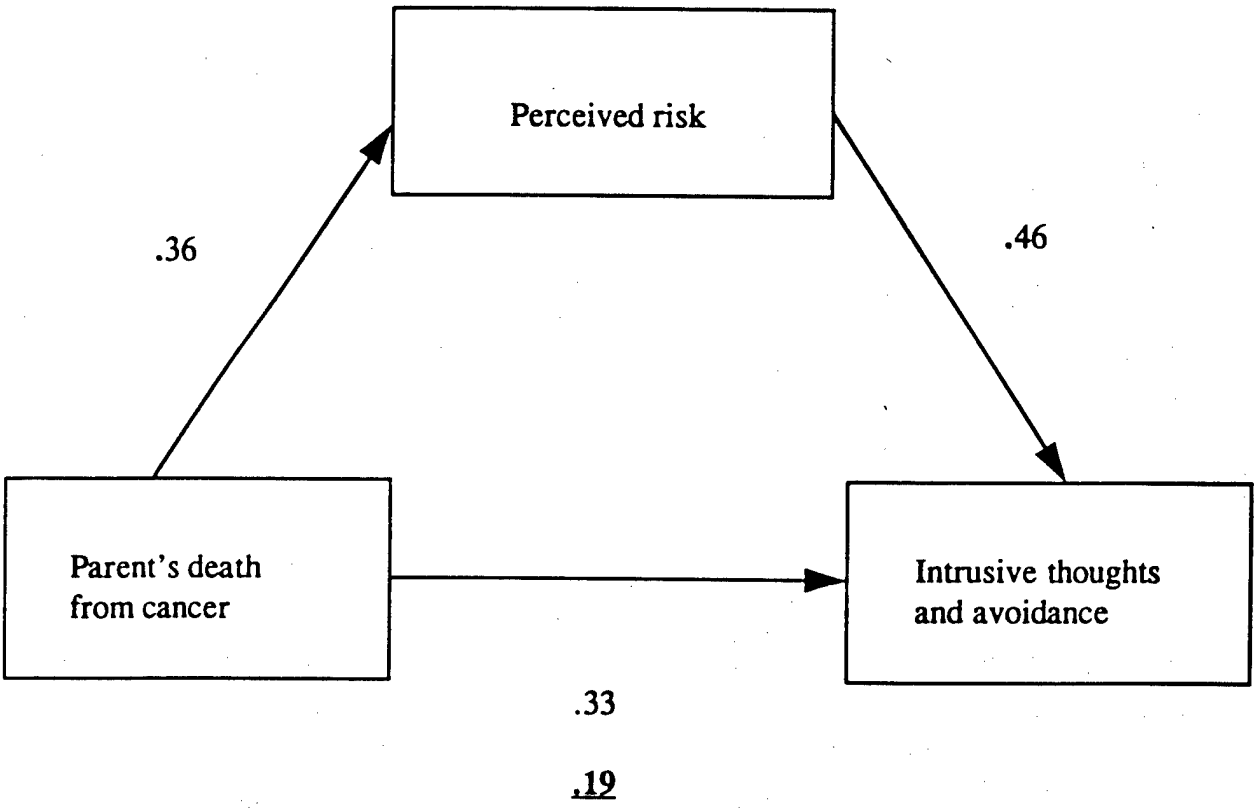

=Risk Subgroup 1
=Risk Subgroup 2
=Comparison Group
Impact of Event Scale (IES)
25.0
20.0
15.0
10.0
5.0
0.0
Assessment Day 1
Assessment Day 2

Figure 2


Perceived risk
.36
.46
Parent's death from cancer
Intrusive thoughts and avoidance
.33
.19

# Decision-Making About Genetic Testing Among Women at Familial Risk for Breast Cancer

PAUL B. JACOBSEN, PHD, HEIDDIS B. VALDIMARSDOTTIR, PHD, KAREN L. BROWN, MS, AND KENNETH OFFIT, MD

**Objective:** Recent identification of the breast-ovarian cancer susceptibility gene *BRCA1* and the breast cancer susceptibility gene *BRCA2* have raised the possibility of clinical genetic testing for breast cancer susceptibility. This study examined decision-making about future susceptibility testing among women at familial risk for breast cancer. Based on the transtheoretical model, it was hypothesized that readiness to undergo testing would be related to the ratio between the perceived advantages (pros) and disadvantages (cons) of learning one's susceptibility status. **Methods:** Seventy-four women with one or more first-degree relatives with breast cancer were recruited before a routine mammogram. Participants completed measures assessing readiness to undergo testing, perceived pros and cons of testing, and perceived breast cancer risk. Family history data was used to calculate empiric genetic risk of developing breast cancer. **Results:** Forty-six per cent of participants planned to seek genetic testing as soon as possible, 35% planned to seek testing in the future, and 19% did not plan to seek testing. As expected, greater readiness to undergo testing was associated with a positive decisional balance (pros > cons). Older age and greater perceived risk (but not empiric risk) also were associated with greater readiness. **Conclusion:** The readiness of many women to seek breast cancer susceptibility testing can be attributed, in large part, to their perceptions that the advantages outweigh the disadvantages. Examination of these perceptions suggests that notification of carrier status may have significant effects on women's psychological well-being and breast cancer surveillance and prevention behaviors.

Key words: genetic testing, breast cancer, decision-making, transtheoretical model.

## INTRODUCTION

Epidemiologic data suggest that 5% to 10% of all cases of breast cancer are attributable to one or more susceptibility genes that are inherited in an autosomal dominant fashion (1, 2). The locations of two such genes have been identified recently. A major breast-ovarian cancer susceptibility gene, known as *BRCA1*, was mapped by linkage to chromosome 17 in 1990 (3) and was isolated by a positional cloning strategy in 1994 (4). A second gene predisposing to breast cancer, labeled *BRCA2*, was identified on chromosome 13 by linkage analysis (5) and also has been isolated recently (6). Available data suggest that women who inherit *BRCA1* mutations have an 80% to 90% lifetime risk of developing breast cancer and an increased risk of developing ovarian cancer (7). Inheritance of *BRCA2* mutations also confers a high risk of developing breast cancer, but not necessarily an increased risk of developing ovarian cancer (6).

With the recent isolation of the *BRCA1* and *BRCA2* genes, it is becoming possible to test individual family members affected by breast or ovarian cancer to determine their carrier status. Once a mutation has been established in an affected family member, unaffected family members then can be tested to determine their carrier status. Once the full spectrum of *BRCA1* and *BRCA2* mutations is identified, it may be possible to determine genetic susceptibility to breast cancer solely by testing unaffected individuals (8).

These developments are expected to lead to a considerable demand for genetic susceptibility testing among women with family histories of breast cancer (7). Three studies have examined this issue by assessing interest in genetic testing among women at familial risk for either breast or ovarian cancer. Lerman et al. (9) examined interest in *BRCA1* testing among 112 women who had at least one first-degree relative diagnosed with ovarian cancer. Seventy-five per cent of this sample reported they would "definitely" want testing and 25% said they would "probably" want testing. Struewing et al. (10) assessed interest in *BRCA1* testing among 91 women

From the Department of Psychology, University of South Florida, and H. Lee Moffitt Cancer Center, Tampa, Florida (P.B.J.); and the Psychiatry Service (H.B.V.) and Clinical Genetics Service (K.L.B., K.O.), Memorial Sloan-Kettering Cancer Center, New York, New York.

Address reprint requests to: Paul B. Jacobsen, PhD, Department of Psychology, University of South Florida, 4202 E. Fowler Ave., BEH-339, Tampa, FL 33620.

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who were members of "hereditary breast-ovarian cancer families" participating in genetic linkage research at the National Cancer Institute. Seventy-nine per cent of this sample reported they would "definitely" want testing and 16% said they would "probably" want testing. Most recently, Lerman et al. (11) assessed interest in genetic testing for breast cancer susceptibility among 105 women who were first-degree relatives of breast cancer patients. Ninety-one per cent of this sample indicated that they would want testing.

These same studies also examined women's reasons for wanting or not wanting to be informed of their genetic susceptibility status. The most commonly cited reasons for wanting testing were: to learn whether one's children are at risk (9–11), to increase use of screening methods (9–11), to take better care of oneself (10, 11), and to be reassured (12). The most commonly cited reasons for not wanting testing were: worries about insurability (10, 11), concerns about test accuracy (11), and worries about emotional reactions (11).

The purpose of the present study was to examine the relation between women's interest in testing and their reasons for wanting or not wanting to be informed of their genetic susceptibility status. To do so, the study used two constructs included in the transtheoretical model of behavior change (13, 14). This model has been presented as an integrative and comprehensive theory of behavior change with potentially wide applicability (15).

The first construct borrowed from the model is behavioral stage of adoption. Previous research (15, 16) has identified a sequence of stages through which people are likely to proceed before adopting new health behaviors such as quitting smoking or going for routine mammograms. These stages include: precontemplation (presently not performing the behavior and not intending to start in a given time period), contemplation (presently not performing the behavior but considering starting in a given time period), and preparation (taking the first steps to change behavior). In the present study, assessment of behavioral stage of adoption required modification inasmuch as genetic testing is neither an ongoing behavior (eg, smoking cessation) nor a recurring behavior (eg, mammography screening). Moreover, genetic testing for breast cancer susceptibility is not currently available on a widespread basis. To address these issues, stage of adoption was operationalized by asking participants to imagine that an individually administered genetic test for breast cancer susceptibility was currently available and to indicate their readiness to take such a test. Participants could indicate that they planned to take the test as soon as possible (preparation), planned to take the test in the near future (short-range contemplation), planned to take the test but not in the near future (long-range contemplation), or did not plan to take the test (precontemplation).

The second construct borrowed from the transtheoretical model is decisional balance. In previous research, this construct has been measured by assessing the relative strength of the perceived advantages (pros) and disadvantages (cons) of adopting a target behavior (17). Based on previous research using the transtheoretical model (15), it was hypothesized that women who did not plan to undergo genetic testing would have a negative decisional balance (cons > pros) and that women who planned to undergo genetic testing as soon as possible would have a positive decisional balance (pros > cons). Women who planned to be tested sometime in the future were expected to have a decisional balance close to the neutral or zero point of pros equaling cons.

In addition to testing hypotheses based on the transtheoretical model, the present study explored the relation of perceived breast cancer risk as well as medical and demographic factors to readiness to undergo genetic testing. With regard to demographic factors, we examined whether age, marital status, or level of education were related to readiness. With regard to medical factors, we examined whether a statistical estimate of genetic risk (16) or previous history of breast biopsy were related to readiness. These factors were selected for study based on a review of the literature on genetic testing for heritable cancers (9–12, 18).

## METHODS

### Subjects

Participants were recruited from three mammography screening programs in New York City. To be eligible for the current study, women attending these programs had to: a) be 18 years of age or older; b) be able to read and write English; c) have no prior history of breast or ovarian cancer; d) have one or more first-degree relatives (mother, sister, or daughter) diagnosed with breast cancer; e) be scheduled for a routine mammogram within the next week; and f) provide written informed consent for study participation. Ninety-four women meeting these criteria were invited to participate in the current study and 82 agreed. Among women who declined to participate ($N = 12$), most cited "lack of time" as the principal reason. Eight women provided incomplete data; thus, results are reported for 74 women (Site A = 48, Site B = 12, and Site C = 14). Women who provided complete data did not differ from women who provided incomplete data in terms of

age, marital status (married/not married), education (high school or less/college), or prior history of breast biopsy (yes/no) ($p \geq .25$).

### Procedure

Potential participants were identified using each clinic's computerized appointment tracking system. Approximately 1 week before her scheduled mammogram, each potential participant was contacted by telephone and given a description of the study procedures. Women interested in participating subsequently met with a research assistant in the clinic waiting area when they arrived for their scheduled mammogram. At this time, the study was described again and written informed consent was sought. Women who provided informed consent then completed a set of questionnaires in the clinic waiting area. Questionnaires relevant to the present study are described below.

### Measures

*Demographic Questionnaire.* Age, education, race/ethnicity, and marital status were assessed using a standard self-report form (19).

*Medical Chart Review.* Medical charts were reviewed before recruitment to determine whether participants met the eligibility criteria of having a first-degree relative with breast cancer and not having a personal history of breast or ovarian cancer. After recruitment, medical charts were reviewed again to determine whether participants had a prior history of breast biopsy and to calculate participants' empiric genetic risk for breast cancer. At the time of their enrollment in each screening program, women provided information about the occurrence of breast cancer and the age of onset of breast cancer in both their first-degree and second-degree relatives. This information was updated at the time written informed consent was obtained and was converted into an empiric genetic risk score using tables derived from a population-based case-control study of breast cancer development (16). The resulting scores represent the probability (expressed in percentages) that each participant will develop breast cancer by age 79 years.

*Perceived Risk of Breast Cancer Scale.* Perceived risk was assessed by having participants rate from 0 (not at all likely) to 100 (extremely likely) the likelihood that they would ever develop breast cancer (19).

*Readiness Scale.* Participants read the following description adapted from a previous study (9) before rating their readiness to undergo genetic testing for breast cancer:

"In a small number of families, several family members develop breast cancer, often at younger ages. Scientists believe that, in some of these families, women who develop breast cancer have inherited a particular gene that makes them susceptible to cancer. This gene is passed down from generation to generation in these families. Some family members will inherit the gene and others will not. In the near future, it may become possible to perform a blood test to determine which members of these families have this breast cancer gene. A woman who has the gene would have an extremely high risk of developing breast cancer in her lifetime. A woman who didn't have the gene would have the same risk of developing breast cancer as a woman with no family history of breast cancer."

After reading this statement, participants were instructed to imagine that the test was currently available and to indicate what their plans would be. Response options were: a) I plan to take the test as soon as possible (within the next 30 days); b) I plan to take the test sometime in the near future (within the next 6 months); c) I plan to take the test, but not in the near future (not within the next 6 months); d) I do not plan to take the test within the next 6 months, but I may change my mind; or e) I do not plan to take the test within the next 6 months and I am not likely to change my mind.

*Decisional Balance Scale for Breast Cancer Genetic Testing.* A self-report scale was administered in conjunction with the Readiness Scale to assess perceptions of the potential advantages (pros) and disadvantages (cons) of undergoing genetic testing for breast cancer. The scale consisted of 21 items (10 pros, 11 cons) described as, "a list of issues a woman might consider in deciding whether or not to take the genetic test described above." Items were drawn from interviews with women at familial risk for breast cancer, discussions with genetic counselors working at a major cancer center, and reviews of publications describing psychosocial issues in genetic counseling and testing for heritable breast cancer (7, 12). Participants rated the degree to which they agreed or disagreed with each item on a 5-point scale (1 = strongly disagree, 3 = neither agree or disagree, 5 = strongly agree). Ratings of potential advantages were summed to yield a total pros score and ratings of potential disadvantages were summed to yield a total cons score. Reliability analysis indicated that the pros and cons scales were internally consistent ($\alpha$ coefficients = .80 and .64, respectively). Correlational analysis suggested that the two scales were statistically independent of each other ($r = -.15$, $p = .21$). As in previous research (17, 20) raw scores for the pros and cons scales were converted into standard $T$ scores (mean = 50, SD = 10) to provide a common metric. A summary decisional balance measure was then created by subtracting the cons $T$ scores from the pros $T$ scores (20).

## RESULTS

### Sample Characteristics

The participants had a mean age of 44 years (SD = 6.09, range = 32 to 59). Ethnic/racial characteristics were: Caucasian, 69; African-American, 2; Hispanic, 1; Asian, 1; and other, 1. Fifty-six of the participants were married, 6 were divorced or separated, 1 was widowed, and 11 were never married. Fifty-nine participants had a college degree, 13 had attended college but not graduated, and 2 had not attended college. Twenty-nine participants (39%) had previously undergone a breast biopsy and, in all cases, the results had yielded no evidence of malignancy. The average participant was estimated to have an 18% probability of developing breast cancer by age 79 (SD = 8.91, range = 11 to 41) because of her family history of breast cancer.

### Readiness to Undergo Testing

If an individually administered test for genetic susceptibility to breast cancer were currently avail-

able. 46% of participants ($N$ = 34) would seek testing as soon as possible (within the next 30 days), 30% ($N$ = 22) would seek testing in the near future (within the next 6 months), and 5% ($N$ = 4) would seek testing in the more distant future. Sixteen per cent ($N$ = 12) would not seek testing but thought they might change their minds, and the remaining 3% ($N$ = 2) would not seek testing and thought they were unlikely to change their minds. In subsequent analyses, participants were divided into three groups: those who planned to seek testing as soon as possible ($N$ = 34); those who planned to seek testing in the future ($N$ = 26); and those who did not plan to seek testing ($N$ = 14).

## Perceived Pros and Cons of Testing

The most commonly perceived pros and cons were identified by tabulating the percentage of women who agreed (4) or strongly agreed (5) with each decisional balance item. Five pros were endorsed by more than 50% of participants (Table 1). The majority of women thought that knowing they *carried the gene* would: help their female relative decide whether to undergo testing, motivate them to perform breast self-examination more frequently, help them decide whether to go for more frequent mammograms, and help them decide whether to undergo preventive surgery. The majority of women also thought that knowing they *did not carry the gene* would reduce their concerns about developing breast cancer.

Two cons were endorsed by more than 50% of participants (Table 2). The majority of women thought that knowing they *carried the gene* would increase their concerns about developing breast cancer and would cause them to worry more about female relatives who might also be carriers.

## Factors Associated with Readiness to Undergo Testing

Statistical analyses were conducted to examine the relation of demographic, medical, and psychosocial factors to readiness to undergo genetic testing for breast cancer (Table 3). $\chi^2$ analyses were performed for categorical measures (eg, marital status) and one-way analyses of variance were performed for continuous measures (eg, age). As a follow-up to significant one-way analyses of variance, pairwise mean comparisons were conducted (using the least

**TABLE 1. Perceived Pros of Genetic Testing**

| Pros | Agree or Strongly Agree |
|---|---|
| My concerns about developing breast cancer would be reduced if I knew I did not carry the gene. | 82% |
| If I were found to carry the gene, it would help my daughter(s) or sister(s) decide whether to undergo genetic testing. | 81% |
| Knowing that I carry the gene would motivate me to perform breast self-examination more frequently. | 77% |
| Knowing that I carry the gene would help me decide whether to go for more frequent mammograms. | 66% |
| Knowing that I carry the gene would help me decide whether to undergo preventive surgery. | 64% |
| My sense of uncertainty about the future would be reduced if I knew whether or not I carried the gene. | 49% |
| Knowing whether or not I carry the gene would increase my sense of personal control. | 45% |
| Knowing whether or not I carry the gene would help me make important life decisions (eg, getting married, having children). | 42% |
| Knowing that I do not carry the gene would greatly improve my quality of life. | 41% |
| Knowing that I do not carry the gene would improve how I feel about myself. | 30% |

**TABLE 2. Perceived Cons of Genetic Testing**

| Cons | Agree or Strongly Agree |
|---|---|
| My concerns about developing breast cancer would increase if I knew that I carried the gene. | 85% |
| Knowing that I carry the gene would cause me to worry more about other family members who could be carriers (eg, mother, sisters, daughters). | 72% |
| Knowing that I do not carry the gene would not be helpful since I could still develop breast cancer. | 39% |
| Knowing that I do not carry the gene would not reduce my concerns about developing breast cancer. | 38% |
| If I were found to carry the gene, it would jeopardize my insurance coverage or lead to problems with my employers. | 34% |
| Knowing that I carry the gene would leave me in a state of hopelessness and despair. | 27% |
| Knowing that I carry the gene would worsen my quality of life. | 20% |
| I feel I already know my chances of getting breast cancer, so I wouldn't learn anything more from being tested. | 15% |
| If I were found to carry the gene, it would lead to marital or family problems. | 7% |
| Testing is not worthwhile because it could yield inconclusive results about whether I carry the gene for breast cancer. | 5% |
| If I were found to carry the gene, it would cause others to view me negatively. | 5% |

TABLE 3. Relation of Demographic, Medical, and Psychosocial Variables to Readiness to Undergo Genetic Testing

| Variables | Readiness | | |
|---|---|---|---|
| | Do not Plan to be Tested ($N$ = 14) | Plan to be Tested in the Future ($N$ = 26) | Plan to be Tested as Soon as Possible ($N$ = 34) |
| Demographic | | | |
| Mean age (and SD)[a] | 41.77 (6.01)*[b] | 42.07 (5.82)* | 45.54 (5.92)** |
| Education (college/total) | 12/14 | 22/26 | 25/34 |
| Marital status (married/total) | 12/14 | 16/26 | 28/34 |
| Medical | | | |
| Previous biopsy (yes/total) | 4/14 | 9/26 | 16/34 |
| Mean empiric genetic risk (and SD) | 16.88 (8.67) | 16.82 (7.58) | 20.39 (9.75) |
| Psychosocial | | | |
| Mean perceived risk (and SD)[c] | 53.93 (27.47)* | 60.00 (22.58)* | 73.12 (19.23)** |
| Mean pros T score (and SD)[d] | 42.34 (9.42)* | 47.95 (8.56)* | 54.72 (8.92)** |
| Mean cons T score (and SD)[e] | 60.97 (9.74)* | 49.13 (9.62)** | 46.15 (6.85)** |
| Mean decisional balance (and SD)[f] | −18.63 (12.91)* | −1.18 (11.39)** | 8.57 (10.94)*** |

[a] $F(2,71) = 3.39$, $p = .04$.
[b] Within rows, cells with different numbers of asterisks are significantly different ($p < .05$).
[c] $F(2,71) = 4.70$, $p = .01$.
[d] $F(2,71) = 10.70$, $p < .0001$.
[e] $F(2,71) = 15.39$, $p < .0001$.
[f] $F(2,46) = 28.06$, $p < .0001$.

significance difference test) to identify specific subgroup differences.

With regard to demographic factors, results showed that readiness was related to age but not to education or marital status. Follow-up analyses indicated that the women who planned to be tested as soon as possible were older than the women who planned to be tested in the future and the women who did not plan to be tested. With regard to medical factors, results indicated that readiness was not related to either previous history of breast biopsy or empiric genetic risk.

With regard to psychosocial factors, results showed that readiness was related to perceived risk. The women who planned to be tested as soon as possible perceived themselves to be at greater risk for breast cancer than the women who planned to be tested in the future and the women who did not plan to be tested. Results also showed that readiness was related to the perceived pros and cons of genetic testing and to the summary decisional balance measure. Subgroup analysis of pros scores indicated that the women who planned to be tested as soon as possible perceived more advantages than the women who planned to be tested in the future and the women who did not plan to be tested. Subgroup analysis of cons scores indicated that the women who did not plan to be tested perceived more disadvantages than the women who planned to be tested in the future and the women who planned to be tested as soon as possible. Subgroup analysis of the decisional balance measure scores indicated that the women who planned to be tested as soon as possible had a more positive decisional balance (pros > cons) than the women who planned to be tested in the future and the women who did not plan to be tested. Furthermore, women who planned to be tested in the future had a more positive decisional balance (pros > cons) than women who did not plan to be tested.

To determine the relative strength of pros and cons within each readiness subgroup, mean pros and cons scores were directly compared using paired $t$ tests. Among women who planned to be tested as soon as possible, mean pros scores were significantly greater than mean cons scores, $t(33) = 4.57$, $p<.0001$. Among women who planned to be tested in the future, mean pros and cons were not significantly different, $t(25) = -.53$, $p = .60$. Finally, among women who did not plan to be tested, mean cons scores were significantly greater than mean pros scores, $t(13) = -5.40$, $p<.0001$.

In light of results indicating that readiness to undergo genetic testing was related to age and perceived risk as well as decisional balance, a multivariate approach was used to determine the unique contribution of decisional balance to prediction of readiness scores. Specifically, a hierarchical multiple logistic regression analysis of readiness scores was conducted in which decisional balance was entered into the model after accounting for the predictive value of age and perceived risk (Table 4).

TABLE 4. Logistic Regression Analysis of Readiness to Undergo Genetic Testing

| Variable Entered | Parameter Estimate | SE | Wald $\chi^2$ | $p$ |
|---|---|---|---|---|
| Age | −0.09 | 0.05 | 4.01 | .05 |
| Perceived risk | −0.03 | 0.01 | 5.47 | .02 |
| Decisional balance | −0.11 | 0.02 | 21.61 | <.0001 |

$\chi^2$ for covariates (3 $df$) = 47.66, $p < .0001$.

After controlling for the predictive value of the other two variables, consideration of the summary decisional balance score significantly improved the ability of the model to predict readiness to undergo genetic testing.

## DISCUSSION

In this discussion, we begin by summarizing what was learned about potential demand for genetic testing for breast cancer susceptibility. Next, we consider the utility of decisional balance and other variables for predicting readiness to undergo genetic testing among women at familial risk. Finally, we explore the implications of the study for clinical programs that plan to offer genetic counseling and testing to women at familial risk for breast cancer.

Future demand was estimated in the present study by asking women to imagine that an individually administered genetic test to determine breast cancer susceptibility was currently available and to indicate whether and when they planned to be tested. Eighty-one per cent of the women stated they would plan to be tested. This figure is consistent with results of previous research that 91% to 100% of women with an affected first-degree relative were interested in genetic testing for breast or breast-ovarian cancer susceptibility (9, 10). Among the 81% of participants who stated they planned to be tested, 35% indicated that they would not seek testing as soon as possible. Previous research using the transtheoretical model suggests that this subgroup includes individuals who are likely to be tested within a year as well as individuals who are likely to still be contemplating testing a year later (21). The future behavior of the 19% of women who stated they did not plan to be tested is also uncertain because most of these women indicated they might reconsider their decisions. Taken together, these figures suggest that approximately 50% of women with a first-degree relative affected by breast cancer will immediately seek testing when it becomes widely available. Whether or not demand for genetic testing will greatly exceed 50% among women at this level of familial risk remains unclear.

Findings regarding the relation of empiric risk and perceived risk to readiness to undergo genetic testing were consistent with earlier research. In previous work, no relation was observed between genetic risk (measured in terms of genetic similarity to the affected relative) and interest in testing (10). Similarly, the present study found that empiric genetic risk based on family history of breast cancer (16) was unrelated to readiness to undergo genetic testing. Previous research also indicated that women who perceive themselves to be at higher risk for breast cancer express greater interest in *BRCA1* testing (9, 10). Likewise, in the present study, women who planned to be tested as soon as possible perceived themselves to be at greater risk than women who planned to be tested in the future or women who did not plan to be tested.

Of principal interest in the present study was the possible relation between the perceived pros and cons of testing and readiness to undergo genetic testing. Results confirmed the hypothesis, based on the transtheoretical model, that decisional balance (ie, the relative strength of pros and cons) would predict readiness. These findings are consistent with previous research (15) on the relation of decisional balance to adoption of other health behaviors such as smoking cessation, sunscreen use, and mammography screening. In general, these studies indicate that a negative decisional balance (cons > pros) characterizes individuals who are in the precontemplation stage and a positive decisional balance (pros > cons) characterizes individuals in the preparation or action stages of adopting a health behavior.

In addition to predicting readiness to undergo testing, assessment of pros and cons yielded considerable information about the perceived advantages and disadvantages of genetic testing for breast cancer susceptibility among women at familial risk. With regard to the perceived advantages, the majority of women agreed that learning their genetic carrier status would motivate them to practice breast-self-examination more frequently, help them decide whether to go for more frequent mammograms or undergo preventive surgery, reduce their concerns about developing breast cancer, and help their first-degree relatives decide whether to undergo genetic testing. These findings suggest that providing genetic testing for breast cancer susceptibility to women at familial risk may have several benefits. First, it may encourage these women to increase their surveillance behavior. Second, it may aid these women in their decision-making about either pro-

phylactic mastectomy or oophorectomy. Third, it may assist the first-degree relatives of these women with their decision-making about genetic testing. And fourth, for individuals found not to be carriers of mutated genes, testing may relieve the heightened psychological distress that seems to be common among women at familial risk for breast cancer (19, 22, 23).

As stated previously, women in the present study perceived relatively few disadvantages associated with genetic testing for breast cancer susceptibility. The only disadvantages perceived by a majority of women were that learning their genetic carrier status would increase their concerns about developing breast cancer and cause them to worry more about other family members who could be carriers. These findings are consistent with the views of experts who have warned about the possible negative psychological consequences of informing women of their genetic carrier status (7, 12). In addition, they provide empirical support for the view that women undergoing genetic testing should receive psychological counseling to prevent or ameliorate these reactions (18).

Several limitations of the present study should be noted. First, the outcome in this study was women's readiness to undergo a hypothetical genetic test for breast cancer susceptibility. Whether future genetic tests will possess the same characteristics as this hypothetical test is unknown. Similarly, the relation of the readiness to undergo testing to actual decisions about genetic testing is unknown. Second, the sample in the present study was predominantly white and well-educated. The results reported here may not be generalizable to women at familial risk who possess different demographic characteristics. Third, the present study was limited to women with at least one first-degree relative diagnosed with breast cancer. Possible interest in genetic testing among those who are not at familial risk or are at lesser familial risk was not assessed.

In conclusion, the results of this study indicate that the decision of many women at familial risk to seek genetic testing is related to their perceptions that the advantages of learning their carrier status outweigh the disadvantages. These results are consistent with the transtheoretical model of behavior change and demonstrate its usefulness in understanding decision-making about genetic testing. Responses to the decisional balance measure further suggest that notification of genetic carrier status is likely to have a significant impact on women's psychological well-being and on their breast cancer surveillance and prevention behaviors. These findings underscore the importance of providing counseling to women who undergo genetic counseling for breast cancer susceptibility in order to prevent adverse psychological reactions and to assist in the evaluation of treatment options.

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